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CLINICAL RESEARCH

AA amyloidosis With Ig-Dominant Staining and Diagnostically Unusual Features

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Introduction: Although serum amyloid A (AA) amyloid may occasionally show nonspecific staining by immunofluorescence (IF), the correct diagnosis can usually be determined by integrating pathologic features and clinical scenario, and using AA amyloid immunohistochemistry (IHC) and/or mass spectrometry. A recent mass spectrometry-based study described false-positive Ig IF staining in a subset of AA amyloid cases.

Methods: We sought to delineate clinicopathologic features of AA amyloid with Ig-dominant staining by using a retrospective review.

Results: AA amyloid with Ig-dominant staining was identified in 10 patients from 5 institutions, representing 1.2% to 4% of AA amyloid kidney biopsies. Evidence of a monoclonal protein was documented in 0% to 2.7% of patients with AA amyloid screened for inclusion, but 30% of those with Ig-dominant staining. The patient population had equal sex distribution and presented at median age of 68.5 years with nephrotic proteinuria and kidney impairment. Etiologies of AA amyloid included injection drug use (30%), autoimmune disease (20%), and chronic infection (10%); 40% had no identified clinical association. On biopsy, heavy chain (co)dominant staining by IF (in 80%), discordant distribution in Ig staining (in 20%), tubulointerstitial nephritis (in 30%), and/or crescents (in 10%) were present. Two of 3 patients with paraproteinemia had concordant heavy and/or light chain dominant staining within the AA amyloid. Two cases were initially misdiagnosed as Ig-associated amyloidosis.

Conclusion: We describe the morphologic spectrum of AA amyloidosis with Ig-dominant staining which may have clinical, laboratory, and pathologic overlap with amyloid light chain (AL), amyloid heavy chain, and heavy and light chain (AHL) amyloidosis.

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The landscape of AA amyloidosis varies by population, location, and era. In developed countries the clinical scenarios classically associated with AA amyloidosis, namely untreated chronic infections associated with environmental exposures and uncontrolled inflammatory or autoimmune disease, have decreased in incidence.[1,2] Conversely, certain behaviors associated with the development of chronic infections, such as intravenous and/or injection drug use–including "skin popping" and "muscling"–are becoming more common.[3,4] AA amyloidosis is also well-described in cancer[5] and periodic fever syndromes,[1] specifically familial Mediterranean fever.[6–8]

AA amyloid is characterized by negative or limited nonspecific staining by standard IF panels. The correct diagnosis can usually be determined by integrating pathologic features with the clinical scenario because many patients have known predisposing conditions for AA amyloid. Rarely, 2 types of amyloid can occur in 1 patient.[9–12] Definitive AA amyloid typing can be achieved by immunostaining (IHC or IF) or mass spectrometry, which represents the gold standard for amyloid typing. A mass spectrometry-based study recently described a false positive Ig IF staining rate of 2.9% for AA amyloid[13] (all with λ light chain), raising concerns about the reliability of amyloid typing by IF. Derived from a national reference laboratory, that

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study encompasses cases selected for mass spectrometry and no further clinical or histologic evaluation was reported.

After an index case was initially misdiagnosed at one of our institutions as AL amyloidosis based on positive IF reactivity for a single light chain and the absence of a clinical etiology for AA (case 1), we sought to better delineate the clinical and pathologic features associated with those cases of AA amyloidosis that present diagnostically challenging or atypical features. We hope that by reporting these data, we can highlight uncommon diagnostic pitfalls which may be encountered in cases of AA amyloid.

METHODS

Renal pathology biopsy databases from Oregon Health and Science University, Columbia University Irving Medical Center, Stanford University, University of Chicago, and University of Washington, were searched for cases with a final or amended diagnosis of AA amyloidosis. Precise time frames varied by center and included years 2000 to 2022. Cases selected for further analysis were those considered atypical or diagnostically challenging to subtype as AA amyloid based on available clinical data and initial biopsy workup. We specifically included cases with Ig-dominant staining by IF, with or without concurrent paraproteinemia or paraproteinuria on serum or urine protein electrophoresis, respectively, and patients with both unusual Ig staining and no known etiology for AA amyloid. For the purposes of this study, cases considered "AL-like" or "AHL-like" were those with Ig IF staining showing ≥2+ staining intensity with 1 light chain or 1 heavy and 1 light chain, respectively, with other immunoreactants demonstrating minimal staining (0 or trace).[13] Heavy or light chain dominant staining included cases which were AL or AHL-like, and additionally those with lower intensity of staining of the dominant Ig (≥1+ intensity), and/or had up to 1+ staining for other immunoreactants. Staining was considered codominant if both 1 heavy and 1 light chain stained were scored as of equal intensity. Negative IF was defined as all IF reactants scoring 0 or trace. Cases with negative IF were excluded, as were those with IgM and/or C3 only staining regardless of staining intensity. Congo Red was positive in all tested cases.

Biopsies had multiple levels cut and stained with Jones methenamine silver, periodic acid Schiff, hematoxylin and eosin, and trichrome. For IF, frozen tissue was stained with antibodies against IgG, IgA, IgM, C3, C1q, fibrin/fibrinogen, κ, λ, and albumin. IgG subclass staining was performed in 1 case and electron microscopy was performed in all cases. All cases had typing by IHC and/or mass spectrometry. IHC for AA (Dako M075901-2 or Biocare Medical PM 125 AA) was performed in 7 cases with variable to strong staining in all, and mass spectrometry for amyloid type was performed in 8 cases (7 at Mayo Clinic, 1 at University of Washington). Raw spectrometry data were not available for review. Two cases were typed by IHC without mass spectrometry; 1 case was in a patient with high clinical suspicion for injection drug use. The other patient had 2 additional biopsies with AA amyloid IHC performed and independently evaluated at other centers; and had negative genetic testing, including for transthyretin, familial Mediterranean fever, tumor necrosis factor receptor-associated periodic syndrome, lysozyme, ApoA1, A2, and fibrinogen alpha.

Clinical history was obtained through discussion with nephrologists and review of the medical record. For proteinuria, spot urine protein-to-creatinine ratio or 24-hour urine protein was analyzed interchangeably given reasonable concordance between methods.[14] Serum κ/λ free light chain ratios were assessed according to standard definitions in patients with preserved estimated glomerular filtration rate (eGFR),[15] and adjusted for eGFR as follows: 0.46 to 2.62 for eGFR 45 to 59; 0.48 to 3.38 for eGFR 30 to 44; and 0.54 to 3.30 for eGFR <30 ml/min per 1.73 m^2.[16] Statistical analyses were performed in Graphpad Prism 7 (San Diego, CA), and summarized as median and range.

RESULTS

AA amyloid with diagnostically challenging features and Ig-dominant staining represented approximately 1.2% to 4% of AA amyloid kidney biopsies, and 0.56% of total amyloid cases at 1 institution. Based on clinical history from pathology reports, evidence of a monoclonal protein at time of biopsy was described in 0%, 2.1%, and 2.7% of patients with AA amyloid screened for inclusion from 3 centers. All study cases preceded routine AA amyloid IHC screening of all biopsies with amyloidosis. At 1 institution, subsequent implementation of AA amyloid IHC screening on nearly all amyloid kidney biopsies, prompted by the study by Gonzalez Suarez *et al.*,[13] did not reveal unsuspected AA amyloid in any case (of 26). Patients with Ig-dominant AA amyloidosis ($n = 10$, Table 1) had an equal sex distribution and presented at median age of 68.5 years, which was statistically significantly older than the median age of other AA amyloid patients screened for inclusion from 1 institution (vs. 53 years, $P = 0.026$). All patients had nephrotic range proteinuria (median 11.8 g, range 4.9–29 g) and most had renal impairment (median creatinine 1.8 mg/dl, range 0.7–6.8 mg/dl). Three patients had paraproteinemia (30%), and 2 had

Table 1. Clinical features of patients with AA amyloid and Ig-dominant staining ($n = 10$)

Variable	Result
Age (yrs)	68.5 (43–80)
Sex	5 (50%) male
Race/Ethnicity	5 (50%) White/4 (40%) Not available/1 (10%) Black
Proteinuria (g)	11.8 (4.9–29)
Creatinine (mg/dl)	1.8 (0.7–6.8)
Paraproteinemia	3 (30%)
Injection drug use	2 (20%)/1 (10%) suspected
Infection	1 (10%) tuberculosis
Autoimmune disease	1 (10%) rheumatoid arthritis/1 (10%) Schnitzler syndrome/1 (10%) multiple sclerosis
Positive autoimmune serology	4 (40%)
Probable etiologies for AA amyloid after workup	4 (40%) Unknown/3 (30%) confirmed or suspected injection drug use/2 (20%) autoimmune/1 (10%) tuberculosis
Prosthetic heart valve and no identified etiology for AA amyloid	2 (20%)

AA, amyloid A.
Results provided in median and range.

Table 2. Pathologic features of kidney biopsies with amyloid A and Ig-dominant staining ($n = 10$)

Variable	Result
Amyloid location	10 (100%) glomerular/9 (90%) vascular/5 (50%) tubulointerstitial
Crescents	1 (10%) case, involving 50% of glomeruli
Acute tubular injury	3 (30%)
Acute tubulointerstitial nephritis	3 (30%)
Ig-dominant staining	10 (100%), including 8 with (co)dominant heavy chain: • 6 IgG: 2 IgGλ, 1 IgGκ, 1 IgG only, 2 with staining variability by amyloid location • 2 IgM: 1 IgMλ, 1 IgMκ • 2 light chain: 1 κ, 1 λ
AL or AHL like immunofluorescence staining	4 (40%) AL like: • 4+ lambda, tr C3 and IgM AHL like: • 4+ IgG and κ, segmental IgA, λ, C3 • 2+ IgM and κ, others negative • 3-4+ IgG and λ, others negative
Staining variability by location of amyloid	2 (20%): • IgG1λ glomerular and κ vascular staining • IgG glomerular and λ vascular staining

AA, amyloid A; AHL, amyloid heavy and light chain; AL, amyloid light chain.

mildly altered κ/λ serum free light chain ratios (1.82 and 2.2, normal reference range 0.26–1.65) though still within suggested limits after adjusting for eGFR. With regard to common associations for AA amyloidosis (Table 1), 3 (30%) had known or suspected injection drug use, 2 (20%) had autoimmune disease, 1 (10%) had chronic infection (tuberculosis), and none had malignancy. The underlying etiology of AA amyloid was unknown in 4 patients (40%) at the time of biopsy and remained uncertain after workup.

On kidney biopsy (Table 2), amyloid was present in glomeruli (100%), blood vessels (90%), and tubulointerstitial (50%) regions. One case (10%) had crescents, and 3 (30%) had acute tubulointerstitial nephritis, including neutrophilic inflammation in 2. By IF, all cases showed Ig-dominant staining. In 2 of 3 patients with paraproteinemia, the Ig-dominant staining was concordant with the patient's paraprotein identified on serum protein electrophoresis. In an additional 2 patients with serum κ free light chain elevations above normal reference range (but within suggested limits after adjusting for eGFR), the IF staining matched the serum κ light chain bias. Specific case details are described below, summarized in Table 3, and illustrated in Figures 1 to 5.

Among 10 cases with heavy and/or light chain-dominant IF staining, 4 cases (40%) were considered AL-like or AHL-like, 2 of which were in patients with paraproteinemia. Two (cases 1 and 9, Figure 1) were initially misdiagnosed as Ig-associated amyloidosis, both of which had strong staining for λ. The first (case 1, Figure 1a–f) had no paraprotein studies available at the time of biopsy, a history of aortic valve repair with no known clinical reason for AA amyloid, and presented with massive proteinuria (26 g) and oliguric acute kidney injury with a creatinine of 6.7 mg/dl (baseline of 0.5 mg/dl). Biopsy showed amyloid with diffuse crescents and AL-like staining. Given impending dialysis requirements, the patient received an initial dose of cyclophosphamide, bortezomib, and dexamethasone for suspected plasma cell neoplasm. Subsequent laboratory studies and bone marrow biopsy were negative for paraproteinemia/paraproteinuria and B-cell/plasma cell neoplasms, respectively; and IHC and mass spectrometry revealed AA amyloidosis. The patient underwent extensive testing, including repeat serologies, imaging, and echocardiograms at 2 referral centers; however, both the etiology and optimal treatment for her AA amyloid remained unknown. At 6 months, after treatment with cyclophosphamide and prednisone, she had clinical improvement in proteinuria (4 g) and serum creatinine (2.0 mg/dl), without adverse effects. The second (case 9, Figure 1g–i) was in a patient with a matching IgGλ paraprotein on serum and urine protein electrophoresis as well as injection drug use. Bone marrow biopsy was not performed or available, the patient did not receive chemotherapy, and she progressed to end-stage kidney disease within 6 years.

Of the other 2 cases with AHL-like staining, 1 was in a man with Schnitzler syndrome (case 5, Figure 2), IgM paraproteinemia, and proteinuria with normal creatinine whose biopsy showed amyloid with IgMκ-restricted (2+) staining and increased κ-positive cells in the interstitium by *in situ* hybridization. The fourth (case 6, Figure 3) was in a patient with longstanding

Table 3. Summary clinicopathologic details of AA amyloid with Ig-dominant staining ($n = 10$)

Case	Summary Clinical Data	Reason for AA Amyloid	Summary Biopsy Features of Amyloid
1	Prosthetic aortic valve, oliguric AKI, nephrotic syndrome	Unknown	AL-like staining (4+ λ; 0 to tr others) with 50% crescents, TIN. Figure 1
2	Prosthetic aortic and mitral valves, CKD, nephrotic syndrome	Unknown	κ dominant staining (1-2+; tr others).
3	Nephrotic proteinuria with preserved eGFR, IgMκ paraproteinemia	Unknown	IgMλ dominant staining (1+; 0 to tr others).
4	Diabetes, HTN, AKI, nephrotic proteinuria	Unknown	IgG heavy chain only staining (1+; 0 others), TIN.
5	Schnitzler syndrome, proteinuria with preserved eGFR, IgM paraproteinemia	Schnitzler syndrome	AHL-like staining (2+ IgM and κ; 0 others). Figure 2
6	Longstanding RA, nephrotic syndrome, +ANA	Rheumatoid arthritis	AHL-like staining (4+ IgG and κ; segmental IgA, λ, C3). Figure 3
7	Pulmonary tuberculosis, AKI, nephrotic proteinuria, +anti-cardiolipin and TTG	Infection (tuberculosis)	IgG1λ-restricted glomerular staining (1 to 2+), with discordant arteriolar amyloid staining (1 to 2+ κ only). Figure 4
8	IVDU, HCV, CKD, nephrotic proteinuria	IVDU	IgG dominant glomerular staining (3+ IgG; 1 to 2+ C3, 0 others), with discordant light chain vascular amyloid staining (2+ λ only). Figure 4
9	IVDU, AIDS, HCV, +cryo, CKD, nephrotic proteinuria, IgGλ paraproteinemia	IVDU	AHL-like staining (3-4+ IgG and λ, 0 others), TIN. Figure 1
10	Multiple sclerosis, suspected IVDU, AKI, nephrotic proteinuria	Suspected IVDU	IgGλ dominant staining (2+; 1+ IgA and C3, others tr). Figure 5

AA, amyloid A; AHL, amyloid heavy and light chain; AKI, acute kidney injury; AL, amyloid light chain; ANA, antinuclear antibody; CKD, chronic kidney disease; Cryo, cryoglobulin; eGFR, estimated glomerular filtration rate; HTN, hypertension; HCV, hepatitis C viral infection; IF, immunofluorescence; IVDU, intravenous and/or injection drug use; RA, rheumatoid arthritis; TIN, acute tubulointerstitial nephritis.
Cases 2 and 6 had elevated k/l free light chain ratios (1.82 and 2.2 respectively), but within acceptable limits after accounting for eGFR.
All cases typed as AA amyloid by immunohistochemistry and/or mass spectrometry except for case 6, in which mass spectrometry revealed predominately AA amyloid with slightly increased Ig κ light chains and γ heavy chains.

rheumatoid arthritis and negative serum and urine protein electrophoresis. Kidney biopsy showed amyloid with bright (4+), smudgy staining for IgG and κ light chain with minimal staining for other immunoreactants, as well as strong AA staining by IHC. Typing by mass spectrometry revealed predominately AA amyloid, with increased Ig κ light chains and γ heavy chains. Serum free light chains were elevated (κ 108 mg/l, λ 49 mg/l; ratio 2.2), but within suggested limits given chronic kidney disease (eGFR: 52 ml/min per

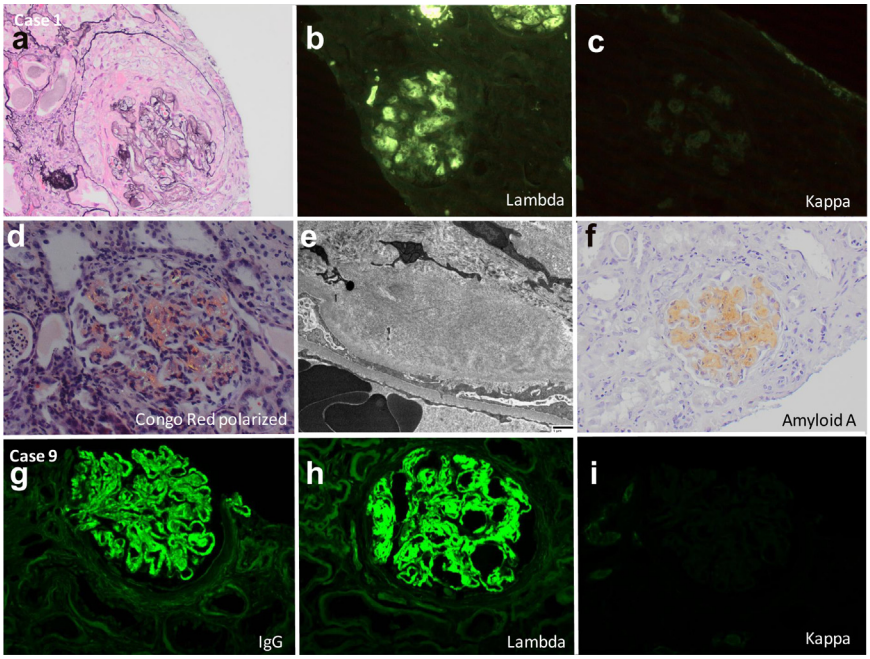

Figure 1. Two cases of AA amyloid initially misdiagnosed as Ig- associated amyloidosis. Case 1 showed (a) amyloid with diffuse crescents (Jones ×200), with strong smudgy staining for (b) λ without significant staining for (c) κ or other immunoreactants; (d) Congo red was positive (×200), (e) electron microscopy showed infiltrative fibrils with a diameter from 7 to 10 nm (direct magnification ×2900), and (f) amyloid A immunohistochemical stain was positive (×200). In case 9, there was bright glomerular and extraglomerular staining for (g) IgG and (h) λ, without significant staining for (i) κ or other immunoreactants. Both were confirmed AA amyloid by immunohistochemistry and mass spectrometry.

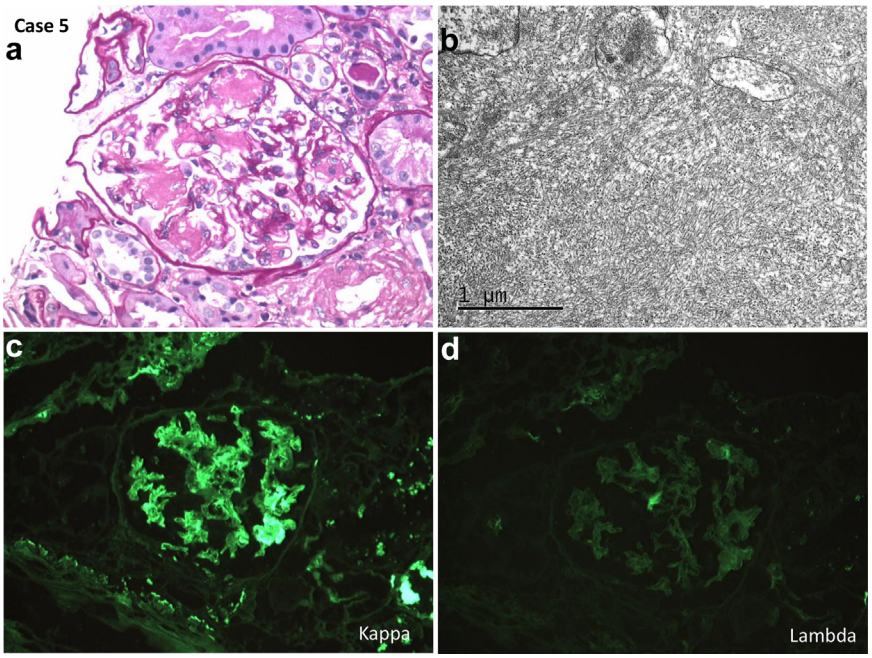

Figure 2. AA amyloid with AHL-like staining in a patient with Schnitzler syndrome and IgM paraproteinemia (case 5), with (a) nodular mesangial expansion by PAS-pale material (Periodic acid Schiff, ×200), (b) infiltrative fibrils by electron microscopy, smudgy staining for (c) κ and IgM (similar to κ, not shown) without significant staining for (d) λ or any other tested immunoreactant.

1.73 m^2). Subsequent bone marrow biopsy was negative for a plasma cell or lymphoid neoplasm, and the increased Ig by mass spectrometry was considered of uncertain significance.

Four cases had heavy and/or light chain-dominant staining (cases 2, 3, 4, and 10), but at a lesser intensity or with higher background staining than those considered AL or AHL-like. These included cases staining

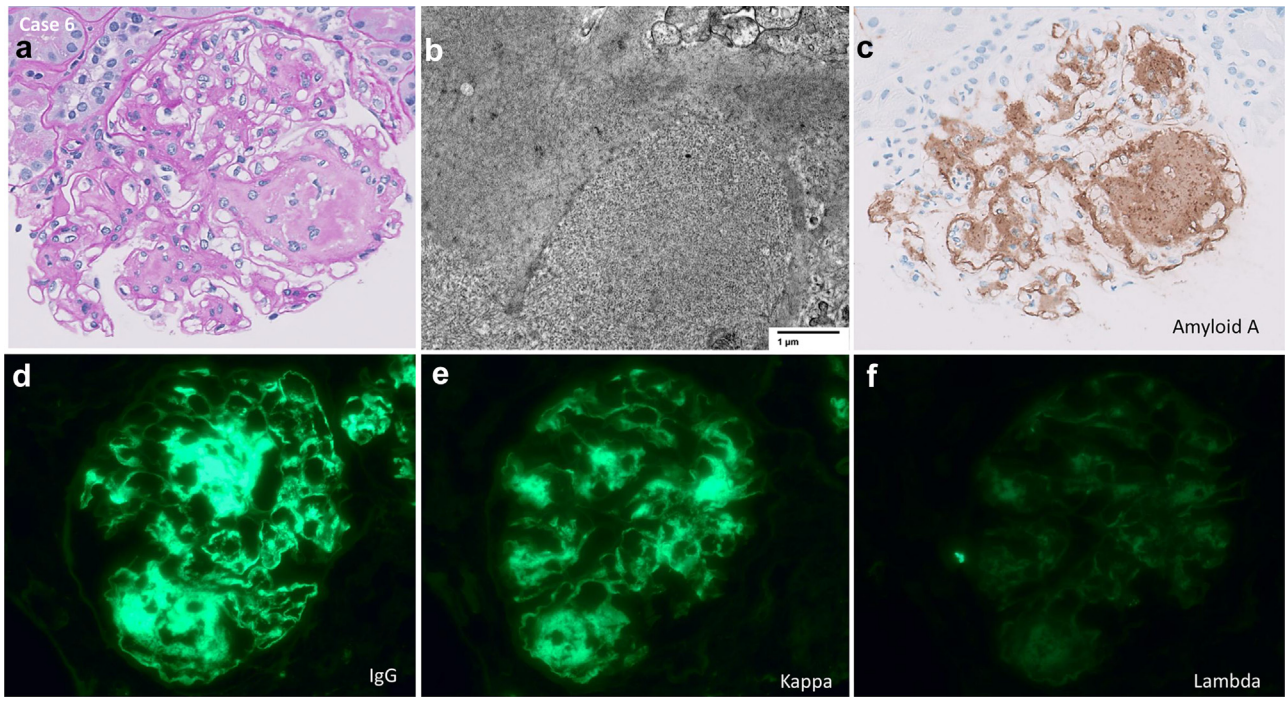

Figure 3. AA amyloid with AHL-like staining in a patient with rheumatoid arthritis (case 6). Kidney biopsy showed (a) nodular mesangial expansion by PAS-pale material (Periodic acid Schiff, ×200), (b) infiltrative fibrils by electron microscopy (direct magnification ×6000), (c) staining for AA amyloid by immunohistochemistry (×200), with bright, smudgy staining for (d) IgG and (e) κ, without (f) significant staining for λ or other immunoreactants. Typing by mass spectrometry revealed predominately AA amyloid, with increased Ig κ light chains and γ heavy chains.

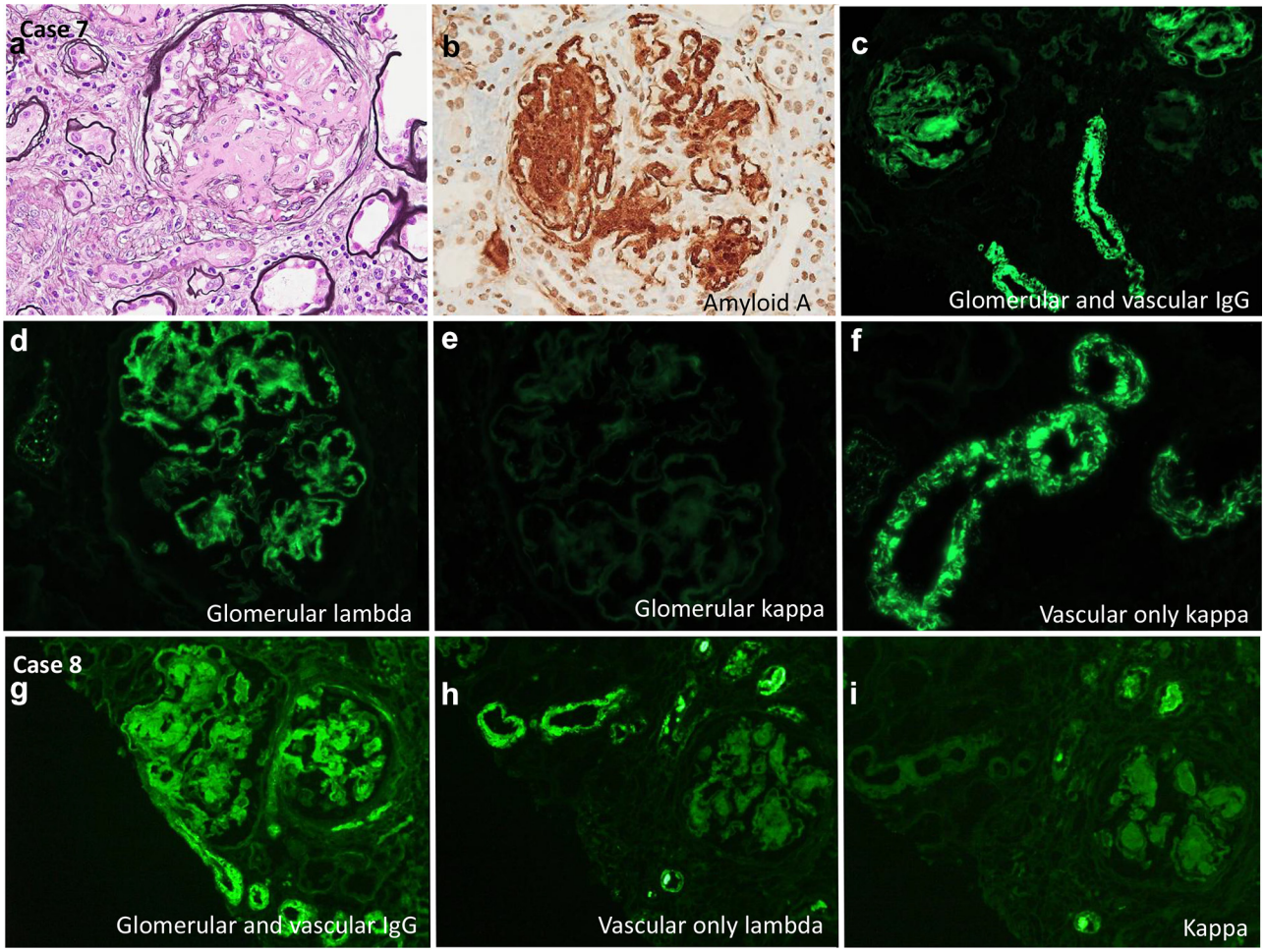

Figure 4. Two cases of AA amyloid with discrepancy in Ig staining by location. Case 7 showed (a) mesangial and capillary wall infiltration by amyloid (Jones stain, ×200) which was (b) positive for amyloid A by immunohistochemistry (×200). (c) Glomerular and vascular amyloid stained for IgG (with IgG1 heavy chain restriction, not shown); glomerular amyloid stained for (d) λ without (e) κ, but arteriolar amyloid stained for (f) κ without λ (λ not shown). Similarly, in case 8, both glomerular and vascular amyloid stained for (g) IgG. (h) Arteriolar but not glomerular amyloid stained for λ, and (i) κ was negative.

predominantly for IgGλ, IgG only, IgMλ (in a patient with IgMκ paraproteinemia), and κ light chain. Three of 4 of these patients had no known or discovered reason for AA amyloid, adding to the potential for misdiagnosis. Together with those with AL or AHL-like staining, 8 of 10 cases had heavy chain (co)dominant staining (6 IgG and 2 IgM), and 4 had λ (co)dominant staining.

Two additional AA amyloid cases had an intriguing pattern of abundant Ig staining but discordant glomerular versus extraglomerular staining. In 1 patient with tuberculosis and negative paraprotein studies (case 7, Figure 4a–f), a discrepancy between glomerular (IgG1λ-restricted) and arteriolar (κ-restricted) IF staining patterns was present. In another patient with injection drug use and negative paraprotein studies (case 8, Figure 4g–i), IgG dominant glomerular staining was discordant with λ-restricted vascular staining. This difference in staining by location prompted further amyloid typing by IHC and mass spectrometry, confirming AA amyloid in both cases

At a median time of 31 (range 6–72) months, follow up data were available for 8 of 10 patients; 4 had progressed to end-stage kidney disease and 4 had stable chronic kidney disease. Treatment was usually conservative, and/or targeted to the underlying disease, with 1 patient each receiving leflunomide, anakinra, or rifampin. Of 4 patients with no known clinical etiology for AA amyloid, 2 had prosthetic cardiac valves (not due to intravenous and/or injection drug use), which were without clinical evidence of complication. Genetic testing was performed on 1 patient and was negative. One of 2 patients initially misdiagnosed as Ig-associated amyloid received cyclophosphamide with sustained improvement in both proteinuria and kidney function, as described above.

DISCUSSION

In this descriptive series, we illustrate cases of AA amyloidosis with Ig-dominant staining by IF and/or in patients with paraproteinemia that were considered

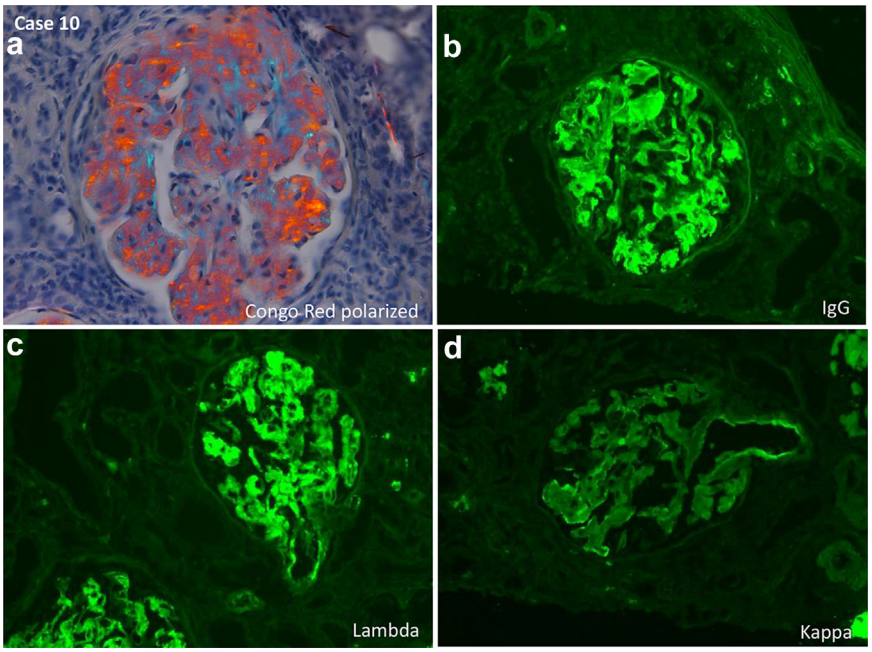

Figure 5. AA amyloid with Ig-dominant staining (case 10) with (a) glomerular amyloid with birefringence under polarized light on Congo Red stain (×200), (b) IgG and (c) λ dominant staining, with (d) trace staining for κ.

diagnostically challenging. In contrast to transthyretin and other types of amyloidosis,[17,18] concurrent paraproteinemia in patients with AA amyloid was infrequent in the overall cases screened for inclusion (up to ∼3%), but was seen in 30% of patients with Ig-dominant staining. These rare cases demonstrate that AA amyloid has the potential to stain similarly to a patient's known paraprotein or elevated serum free light chains. Serum AA protein binds to a remarkably diverse set of ligands,[19] and AA amyloid IHC has a recognized capacity for modest Ig staining and nonspecific reactivity ("stickiness").[20,21] Light chain-biased staining is generally not a diagnostic distractor when integrated with other pathologic and clinical features. Taken together with the older age and lack of apparent etiology for AA amyloid in some patients with Ig-dominant staining, these cases emphasize rare pitfalls in the clinical-pathologic associations commonly applied to amyloid diseases. However, the presence of IgG heavy chain (co)dominant staining, a confounding feature previously observed in AA amyloid,[22] or a discordance in staining characteristics by location (i.e., glomerular vs. vascular) are IF features, which may prompt further amyloid characterization such as AA amyloid IHC testing and/or mass spectrometry.

Although crescents are uncommon in amyloidosis, AA is the most common type associated with crescents. In a review of recently published series and case reports on renal amyloid with crescents, 16 of 21 (76%) reported cases have been associated with AA amyloid, most commonly in patients with rheumatoid arthritis or underlying malignancies.[23–29] The remaining 5 (24%) occurred in AL amyloid,[23,25,26,28] 1 in a patient with a positive anti-neutrophil cytoplasmic antibody. Crescents may be more common in cases of AA amyloid with concurrent glomerular Ig deposition.[21] Therefore, cases of amyloidosis occurring on an inflammatory background, with crescents and/or acute tubulointerstitial nephritis as were observed in 3 of our 10 cases (30%), should also trigger a workup for AA amyloid regardless of IF typing.

Our series included 4 patients with AA amyloidosis and dominant Ig staining in which no clear predisposing condition was known at the time of biopsy nor elucidated upon follow-up clinical investigation. Specifically, there was no injection drug use, chronic infection, rheumatologic disease, malignancy, or periodic fever syndrome. At ages ranging 67 to 80 years, these patients are above most reported ages of familial AA amyloid[30–34]; however, clinical presentations and mechanisms of hereditary AA amyloidosis vary, and a genetic component cannot be excluded. Two patients had prosthetic heart valves, which had no evidence of infection or other clinically apparent complication. Allergy to joint prosthesis has been described in 1 case of AA amyloid[35]; however, subclinical reactions to prosthetic heart valves as a contributor to AA amyloid development have not been reported. Obesity has also been identified as a susceptibility factor for AA amyloidosis[36]; however, this was not specifically evaluated in this study.

This series is focused on AA amyloid cases with Ig-dominant staining and does not examine diagnostic

thresholds for IF staining intensity for amyloid subtyping. Amyloid subtyping practices vary and require integration with multiple clinical and pathologic features, the latter of which are incompletely summarized by IF staining intensity scores. In general, we have a low threshold to consider mass spectrometry in the setting of discrepant clinical or pathologic findings, although resource and technical limitations may prevent subtyping by mass spectrometry in some scenarios. Considering that 80% of cases were identified by pathologist-initiated workup, this series does not provide data on whether routine AA amyloid IHC screening is beneficial.

In addition, findings from this cohort do not reveal the reasons for Ig-dominant staining, hypotheses for which include "stickiness," technical factors, and true increases in Igs within AA amyloid deposits due to undetermined mechanisms. The latter possibility may be considered due to the presence of a paraprotein or mildly altered serum free light chain ratio in 5 patients; however, correspondingly increased Igs were reported by mass spectrometry in only 1 patient (without paraproteinemia or a plasma cell disorder). Raw mass spectrometry data was not reviewed, and further evaluation of cases in which Igs are increased by mass spectrometry may elucidate the biological or clinical relevance of that finding. No patient had convincing evidence of 2 types of amyloid, a rare phenomenon.[9–12]

In summary, we describe the morphologic spectrum of AA amyloidosis with diagnostically challenging features and Ig-dominant staining, which may have clinical, laboratory, and pathologic overlap with AL, heavy chain, or AHL amyloidosis. Concurrent paraproteinemia is more common in these patients and may confound IF staining interpretation. When typing amyloidosis in renal biopsies, pathologic features described herein, heavy chain (co)dominant staining, discrepant Ig staining by location, and crescents, should prompt additional testing for AA amyloid by IHC and/or mass spectrometry.

DISCLOSURE

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