Case Report

The Royal Society of Medicine

Journal of the Royal Society of Medicine Open;
0(0) 1–4
DOI: 10.1177/2054270416640156

Rare and unusual clinicopathologic presentation of renal AL amyloidosis

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Summary
Rarely, renal light chain (AL) amyloidosis may present without significant proteinuria owing to glomerular sparing and amyloid deposition confined to the vasculature and tubulointerstitium.

Keywords
(AL) Amyloidosis, light chains, multiple myeloma, proteinuria, renal amyloidosis

Case report

A 48-year-old nonsmoking Filipino man with a medical history of hypertension, recurrent syncope, and chronic Hepatitis B previously treated with tenofovir and self-administered herbal agents complicated by chronic kidney disease attributed to drug-induced tubulointerstitial disease, presented for follow-up care and was admitted to the hospital for acute on chronic liver and kidney injury. Baseline and admission laboratory values are shown in Table 1. He was jaundiced but otherwise asymptomatic and nonoliguric. Urinalysis showed no proteinuria or haematuria and a spot urine protein to creatinine ratio was 0.6. Abdominal ultrasound demonstrated hepatomegaly without ascites, focal liver lesion, or biliary ductal dilatation; kidneys were slightly enlarged (12.4 and 12.8 cm in length) without stones, masses, or hydronephrosis. Echocardiogram showed sparkling left ventricular acoustic reflections and moderate left ventricular hypertrophy with normal ejection fraction and no restrictive physiology; electrocardiogram did not demonstrate any conduction abnormalities. Serum protein electrophoresis was negative for monoclonal gammopathy but urine protein electrophoresis demonstrated kappa light chains. Serum free kappa light chains were markedly elevated at 915 mg/dL with a kappa/lambda light chain ratio of 59.0. Liver function tests continued to trend upward despite optimal virologic response to entecavir which was started for Hepatitis B treatment, and his kidney function also continued to worsen.

Kidney biopsy showed amorphous deposits expanding the small artery walls and tubular basement membranes (Figure 1(a)) staining positive for Congo Red (Figure 1(b)), with relative sparing of the glomeruli (Figure 1(c)). Immunofluorescence showed dominance of staining of the tubulointerstitial and vascular deposits for kappa light chain (Figure 1(d)). Electron microscopy demonstrated randomly arrayed straight 8–10 nm thick fibrils expanding the interstitium and surrounding interstitial capillaries and atrophic tubules (Figure 1(e)). Liver biopsy also showed Congo Red positive amorphous deposits in the blood vessel walls and within the hepatic sinusoids. Bone marrow biopsy was consistent with plasma cell neoplasm, demonstrating 50–60% atypical kappa predominant plasma cells by immunohistochemistry.

The patient was initiated on treatment with intravenous dexamethasone and bortezomib 0.7 mg/m^2 and received five concurrent treatments of plasmapheresis. Over the ensuing month, he had a decrease in serum free kappa light chains, downtrending liver enzymes, and improvement in kidney function with serum creatinine nadir of 3.8 mg/dL from a peak level of 5.5 mg/dL. Unfortunately, he later suffered a witnessed syncopal episode followed by cardiac arrest resulting in his death.

Discussion

This patient was diagnosed with multiple myeloma presenting as kappa light chain restricted systemic AL amyloidosis with biopsy-proven involvement of the kidney, liver, and bone marrow. We speculate that cardiac involvement was also probable given his history of recurrent syncope; moderate left ventricular hypertrophy in the absence of uncontrolled hypertension; and the presence of sparkling left ventricular acoustic reflections, likely representing myocardial amyloid deposition. Cardiac magnetic resonance imaging with intravenous gadolinium is

Table 1. Baseline and admission laboratory values.

Variables	Baseline	Admission
Hematologic		
White blood cell count, $\times 10^3/\mu L$	9.1	9.9
Differential cell count, %		
Polymorphonuclear cells	5.2	6.7
Lymphocytes	2.7	1.8
Monocytes	0.8	0.8
Hemoglobin, g/dL	13.3	13.5
Hematocrit, %	40.8	39.2
Platelet count, $\times 10^3/\mu L$	252	256
Serum chemistry		
Sodium, mEq/L	139	136
Potassium, mEq/L	4.6	3.9
Chloride, mEq/L	100	101
Bicarbonate, mEq/L	27	24
Urea Nitrogen, mg/dL	21	37
Creatinine, mg/dL	2.1	3.3
Glucose, mg/dL	83	90
Calcium, mg/dL	10.2	10.4
Albumin, g/dL	4.3	3.7
Total protein, g/dL	6.3	6.7
Total bilirubin, mg/dL	0.9	6.9
Aspartate aminotransferase, U/L	62	203
Alanine aminotransferase, U/L	94	196
Alkaline phosphatase, U/L	251	774

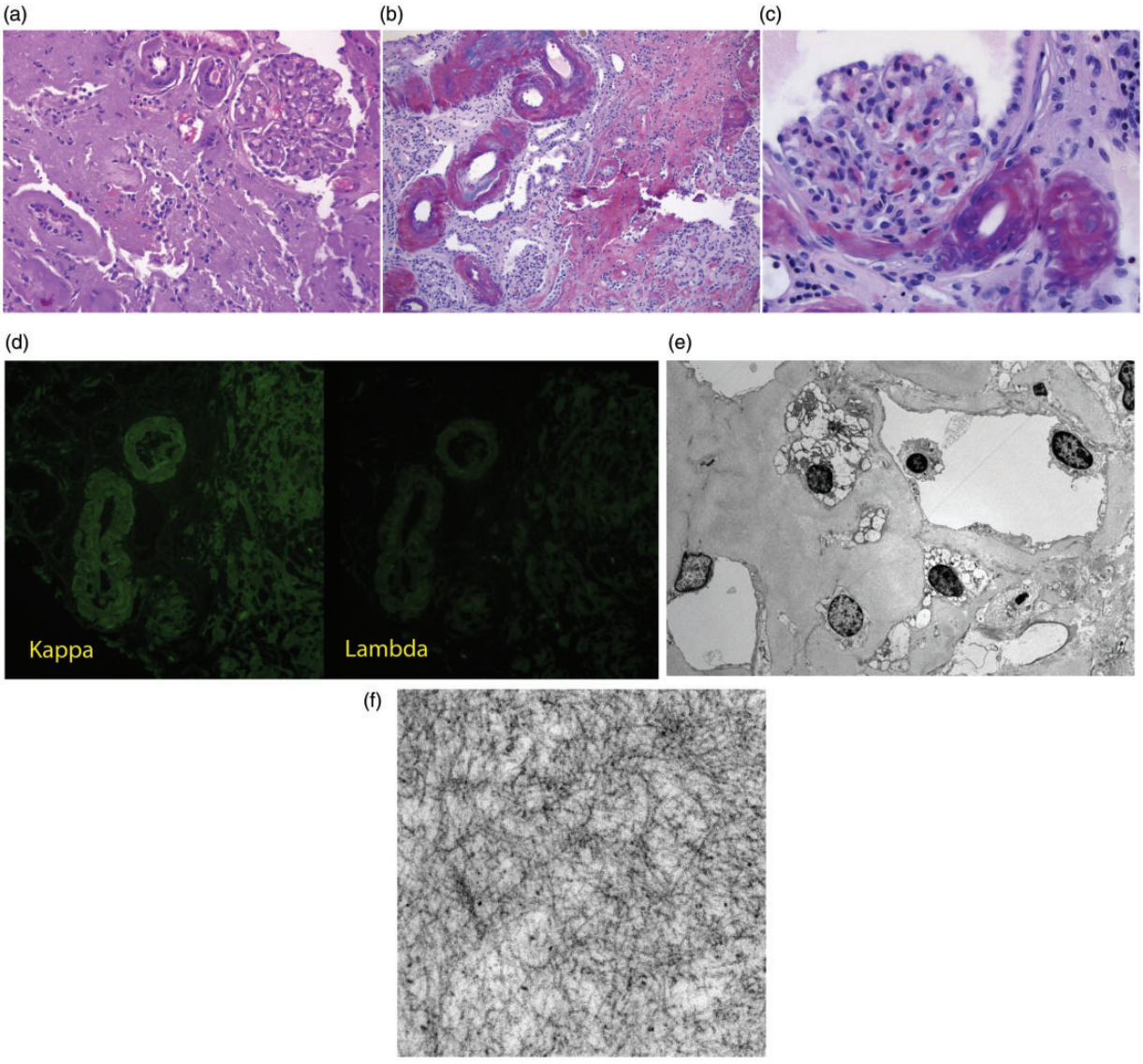
highly sensitive and specific for evaluating amyloid deposition in the myocardial tissue[1] but could not be done in this patient due to reduced renal function and risk of gadolinium-induced nephrogenic systemic fibrosis.[2]

The patient's baseline chronic kidney disease was attributed to tubulointerstitial disease presumably due to past tenofovir and herbal medication exposure.[3] Hepatitis B-induced glomerular disease was thought to be unlikely in the absence of significant proteinuria or active urinary sediment. His baseline liver function test abnormalities were attributed to chronic hepatitis B infection. However, the unexplained persistent rise in liver function tests despite optimal virologic response to entecavir and unclear etiology of acute kidney injury led consulting services to recommend liver and kidney biopsies. Subtle clues in the patient's medical history, such as mild hypercalcemia and history of recurrent syncope, considered in the context of acute and progressive liver and kidney injury, led us to consider the possibility of a plasma cell dyscrasia-induced deposition disease as a unifying diagnosis to explain the multi-organ involvement despite the absence of significant proteinuria which is typically considered a hallmark of that presentation.

Interestingly, the results of our workup and liver and kidney biopsies confirmed our suspicion of AL amyloidosis. Hepatitis B has also been reported as a cause of secondary AA amyloidosis[4] but is uncommon and would not present in association with kappa light chain deposition as evidenced in this patient. Rather, the confirmation of light-chain related amyloid composition in the biopsy tissues was necessary and sufficient to establish the diagnosis of AL amyloidosis[5] as serum free light chains may be elevated in the absence of direct organ involvement.

The kidney is the organ most commonly involved in systemic AL amyloidosis, which occurs in approximately 10–15% of patients with multiple myeloma. The vast majority of these patients present with nephrotic-range proteinuria and a glomerular predominance of renal amyloid deposits consisting of randomly oriented 8–10 nm thick fibrils which stain positive for Congo Red and may demonstrate classically described apple-green birefringence or show anomalous colours under a polarised light source. Renal insufficiency typically occurs later. In the largest clinicopathologic series of 407 renal amyloidosis patients including the AL type, Said et al.[6] reported 97% had glomerular deposits, 56% had arteriolar and arterial deposits, 58% had interstitial deposits, and only 8% had tubular basement membrane deposits. Their 24 h urine protein measurements ranged from 3.4 to 10.0 g. Our case is atypical in that our patient presented without significant proteinuria and had relative sparing of amyloid deposition in the glomeruli, despite the marked elevation of serum free kappa light chains and systemic multi-organ involvement. His renal amyloid deposits were essentially limited to the vasculature and tubular basement membrane with additional interstitial involvement. It should also be noted that AL amyloidosis commonly presents with the predominance of lambda

Figure 1. (a–c) Light microscopy of kidney biopsy specimen shows widening of the interstitium and thickening of the tubular basement membranes by amorphous hyaline material (a), with prominent Congo Red staining of amyloid in the interstitium and (markedly thickened) small artery walls (b), but relative sparing of the glomeruli (c). (d) Immunofluorescence microscopy of kidney biopsy specimen shows a dominance of staining of the interstitial and vascular amyloid for kappa light chain. (e–f) Electron microscopy of kidney biopsy specimen shows finely fibrillar amyloid expanding the interstitium and surrounding interstitial capillaries and atrophic tubules (e) and high magnification (original 15,000×) of the typical randomly arrayed straight fibrils of amyloid, about 8–10 nm thick (f).



rather than kappa light chains but may deviate from this pattern when multiple myeloma is also present as in our case.

The standard treatment of AL amyloidosis is chemotherapy-based and directed against the amyloid-producing abnormal plasma cells. In this case, the proteasome inhibitor bortezomib was used in combination with the corticosteroid dexamethasone based on previous studies which demonstrated rapid and high rates of hematologic and organ response associated with this regimen[7] which also has proven efficacy in the treatment of multiple myeloma.[8] The use of plasmapheresis is controversial but renal improvement has been reported when bortezomib was combined with plasma exchange in patients with myeloma and significantly elevated serum light chains at risk for cast nephropathy.[9] The benefit of autologous bone marrow stem cell transplantation in

patients with AL amyloidosis is uncertain but may improve outcomes in patients with renal involvement.[10]

In summary, AL amyloidosis is an uncommon disorder which may occur in association with multiple myeloma and involve multiple organs, most commonly the kidney. Though patients with renal involvement typically present with nephrotic-range proteinuria and glomerular predominance of amyloid deposits, a small portion may present with amyloid deposition sparing the glomeruli and confined to the tubulointerstitium and/or vasculature. Therefore, AL amyloidosis should not be overlooked in patients whose presentations provide subtle clues pointing to the possibility of a plasma cell dyscrasia, even in the absence of significant proteinuria.

Declarations

Competing interests: None declared

Funding: None declared

Ethical approval: Written informed consent for publication was obtained from patient's spouse.

Guarantor: NJ

Contributorship: AL, AP, and NJ manuscript preparation; CZ histopathology interpretations; ZZ and NJ final review and edit.

Provenance: Not commissioned; peer-reviewed by David Goldsmith.

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