HIVAN is characterized by collapsing FSGS [4]. Though mechanisms by which HIV-1 genes cause nephropathy are not fully known, transgenic rodent models have shown that podocyte-restricted expression of HIV-1 gene products is sufficient for the development of collapsing FSGS [5]. Several reports indicate a role for parvovirus B19 in collapsing FSGS [7]. Parvovirus B19 DNA was also identified in podocytes of patients with FSGS [7]. Collapsing FSGS is a proliferative disease defined by segmental or global wrinkling of the glomerular basement membranes associated with podocyte proliferation [8]. The pathological similarity of FSGS to HBV infection indicates the same mechanism of HIVAN and parvovirus B19-associated nephropathy.

The diagnosis of HBV-associated glomerulonephritis is established by serologic evidence of HBV antigen or antibodies, by presence of glomerulonephritis on kidney biopsy and by demonstration of one or more HBV-related antigens by immunohistochemistry [1]. There are seven cases reported previously, which showed FSGS complicated by HBV infection [2]. Some of them demonstrated HBV antigen in glomeruli or tubular cells by immunostaining technique [2]. However, there is no report which proved HBV antigens or DNA in podocytes. In our case, we used a quite different technique to prove the HBV-DNA in podocytes. After the entecavir therapy, HBV-DNA level in the extraction of podocytes was decreased below the limit of detection. Proteinuria, renal function and pathological findings dramatically improved, paralleling the decreased level of HBV-DNA. The fact that clinical and pathological findings improved paralleling the decreased level of HBV-DNA in podocytes, suggests that HBV infection of these cells could have been responsible for inducing FSGS in this case. This is the first report documenting HBV infection in podocytes. We conclude that refractory FSGS induced by HBV can be effectively treated with appropriate anti-viral agents.

Conflict of interest statement. None declared.

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Atypical presentation of atypical amyloid

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Abstract

Amyloidosis is a group of diseases categorized by precipitation of a group of protein aggregates (amyloid) in tissues, including the kidney, and proteinuria is usually the commonest, though not exclusive, hallmark of clinical presentation. AL and AA are the most commonly recognized forms of amyloidosis involving the kidney, but other forms have been described. We present a case of renal amyloid-

osis due to a novel amyloidogenic protein, leucocyte cell-derived chemotaxin 2, without proteinuria at presentation or on subsequent follow-up.

Keywords: ALECT2; amyloidosis; proteinuria

Introduction

Amyloid is defined as *in vivo* deposited material, distinguished from non-amyloid deposits by its characteristic ultrastructural fibrils [1] and affinity to Congo red stain, with green birefringence under polarized light. It can be confined to the kidney but commonly manifests as a systemic disorder with renal involvement. Systemic amyloidosis involving the kidney is commonly related to monoclonal kappa/lambda immunoglobulin light chain-type (AL) or AA amyloidosis. Other forms of amyloidosis can also have renal involvement (Table 1). Significant proteinuria is routinely documented with presentation, although it can be minimal if amyloid is confined to the tubulointerstitium or vasculature [2]. Amyloidosis should always be considered in the differential diagnosis in adult patients with nephrotic syndrome, and serum and urine immunofixation should be included in the workup. We describe an intriguing case of LECT2 amyloidosis (ALECT2) involving the kidney without proteinuria.

Case

A 52-year-old Sudanese female residing in the United Arab Emirates presented to the renal clinic in July of 2009. In August 2006, her blood urea nitrogen (BUN) and creatinine values were 17 and 1.1 mg/dL, respectively. She was in her usual state of health until June 2009 when she developed generalized fatigue and joint pains involving her big toe and hands. She was prescribed a COX-2 inhibitor by her primary care physician. Subsequent laboratory workup revealed a slightly elevated serum creatinine and positive rheumatoid factor. Serologies for lupus and scleroderma were negative, and urinalysis was normal. Renal ultrasound was unremarkable. She was referred to the renal clinic for further evaluation. Examination revealed a moderately obese hypertensive female with no other physical findings. At that time, BUN and creatinine were 23 and 1.4, respectively. Serum total protein was 7.2 g/dL, albumin 4.3 mg/dL, haemoglobin 10.3 g/dL, ESR 46 mm/h and rheumatoid factor negative. ANA screen was borderline positive at 40 (speckled pattern). Complement levels were normal, and cryoglobulin screen was negative. Serum immunofixation showed no evidence of a monoclonal gammopathy. Complete urinalysis was negative for protein or blood. Urine protein-to-creatinine ratio was 0.16 mg/dL. COX-2 inhibitor was discontinued with no improvement in renal function. Follow-up serum creatinine, in January 2010, was 1.5 mg/dL, and urinalysis was again negative for protein. A renal biopsy was performed in her resident country.

Methods and results

Paraffin-embedded renal tissue was sectioned at 3 μm and stained with H&E, and immunoperoxidase stains for AL kappa, lambda light chains, and AA protein. A 10-μm section was stained positive for Congo red. Light and immune fluorescence microscopic findings were consistent with amyloid (Figure 1A–C) but negative for AL and AA. Ultrathin 100-nm sections were stained and examined on an electron microscope (Philips CM12) that detected fibrils consistent with amyloid (Figure 1D). Liquid chromatography–tandem mass spectrometry with laser microdissection was performed on peptides extracted from Congo red-positive and paraffin-embedded tissue, and showed a

Table 1. Reported forms of amyloidosis

Type	Involved organs	Treatment
AL	Kidney, heart, peripheral nerves and liver	Steroids, melphalan, thalidomide, and high-dose intravenous melphalan chemotherapy with autologous stem cell rescue
AA	Kidney and gastrointestinal tract	Treat the underlying cause (i.e. antibiotics, anti-inflammatory cholchine); eprodisate[a]
TTR (familial polyneuropathy)	Peripheral nerves Heart and kidney Gastrointestinal tract	Liver transplant (can be done in conjunction with other affected organ transplant, i.e. liver plus kidney, or liver plus heart); Diflunisal[b]
AAPO A1	Liver and kidney	Liver and kidney transplant
AAPO A2	Kidney	Renal transplant
AFib	Kidney	Liver and kidney transplant
ALys	Gastrointestinal tract, liver and kidney	Undefined
AGel	Cranial nerves, skin and eye	Undefined
ACysC	Central nervous system	Undefined
ALECT2	Kidney; other manifestations are undefined	Undefined

AL, light chain amyloid; AA, amyloid A; TTR, transthyretin; APO, apolipoprotein; Fib, fibrinogen; Lys, lysozyme; Gel, gelsolin; CysC, cystatin C; LECT2, leucocyte cell-derived chemotaxin 2.
[a]Not FDA-approved, and not available to the general public for the treatment of TTR amyloidosis.
[b]Under efficacy study for amyloidosis treatment.

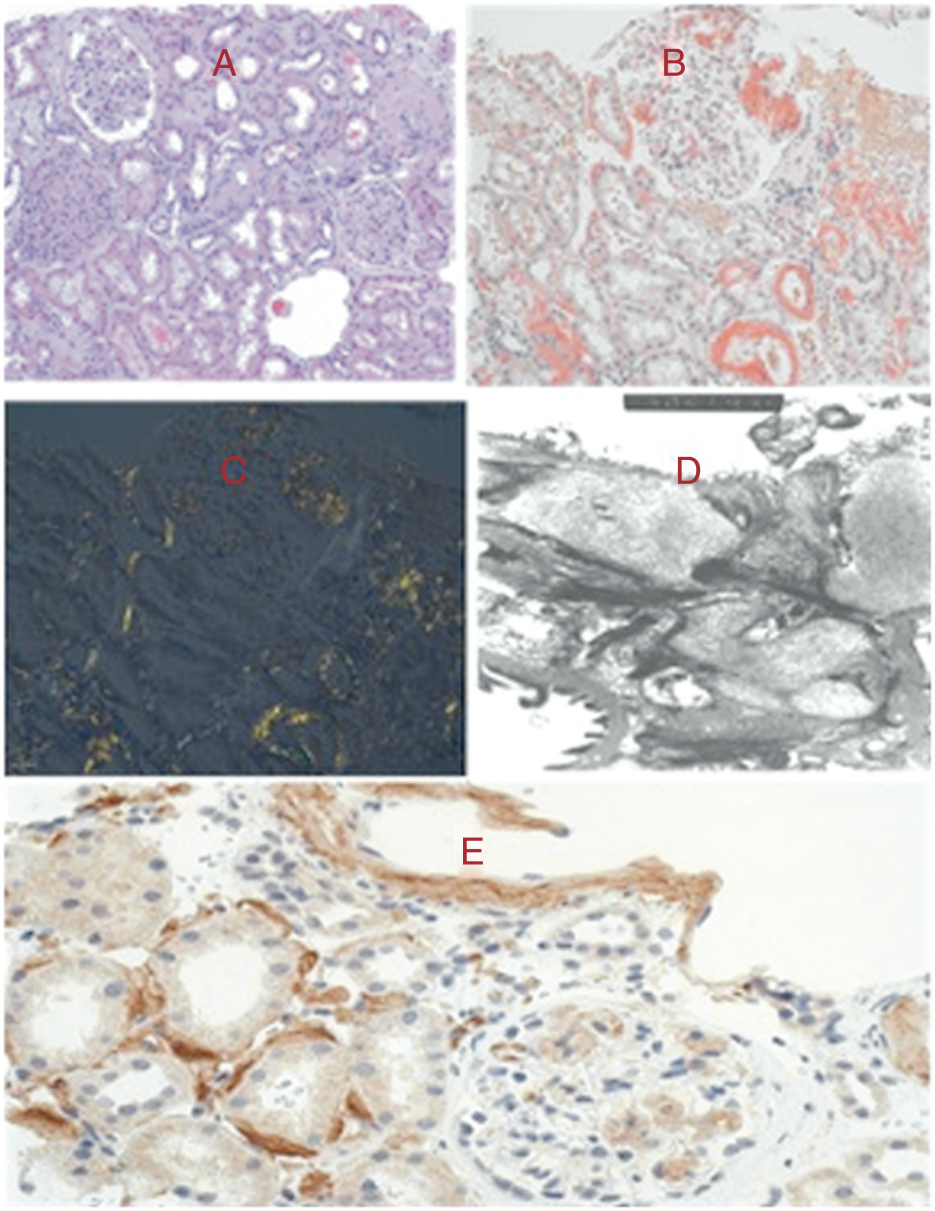

Fig. 1. Pathological diagnosis of renal amyloidosis. (**A**) H&E. Glomeruli ranging from normocellular (top left), with mild (bottom right) and moderate (bottom left) mesangial matrix expansion by eosinophilic material, to a globally sclerosed glomerulus (top right). (**B**) Congo red strongly positive in glomerular mesangium and capillary walls, tubulointerstitium, and vessels. (**C**) Focal red-green circular dichroism on polarization. (**D**) Ultrastructural non-branching fibrils, randomly oriented, 11.2 nm in average thickness, in mesangium and capillary walls. (**E**) Positive immunoperoxidase staining for LECT2 in the glomeruli, mostly in segmental capillary loops, sparsely in mesangium, and largely in the tubular basement membranes, vascular walls, and interstitium.

peptide profile consistent with ALECT2 [3]. The mass spectrometry detected the following tryptic peptides: (K) NAINNGVR(I) ×2, (K)LGTLLPLQK(V) ×3, (R) HGCGQYSAQR(S) ×4, (H)VHIENCDSSDPTAYL(−) ×6 and (K)VYPGIQSHVHIENCDSSDPTAYL(−) ×1, accounting for 30% of the LECT2 amino acid sequence. Subsequently, immunohistochemistry for LECT2 was performed on paraffin sections using a monoclonal antibody raised against recombinant LECT2 protein (Clone 102717, R&D Systems, Minneapolis, MN, USA) with heat-mediated antigen retrieval and polymer-based detection chemistry (Advance, Dako North America, Inc., Carpinteria, CA, USA). The paraffin-embedded amyloid tissue previously typed as LECT2 amyloidosis by mass spectrometry was used as positive control, and cases of AL and ATTR amyloidosis were used as negative controls (Figure 1E). Follow-up serum creatinine, in April 2010, remained stable at 1.5 mg/dL, and urinalysis as well as urine protein-to-creatinine ratio revealed no evidence of proteinuria.

Discussion

We describe a unique case of renal ALECT2 with intriguing presentation of moderate renal dysfunction and

complete absence of proteinuria. A novel amyloidogenic protein, LECT2, was recently described in patients with renal amyloidosis and is being increasingly documented [4]. ALECT2 has not yet been detected in organ systems other than the kidney. The first report of ALECT2 was in a patient who presented with nephrotic syndrome [5]. Our unique case demonstrates a potential pitfall in the diagnosis of amyloidosis and emphasizes the clinical significance of workup in early stages of kidney disease. This is critical for primary practitioners dealing routinely with the bulk of early kidney disease patients, particularly when proteinuria has not yet evolved. Although systemic amyloidosis is rare, with an estimated prevalence of 1:60 000 [6], new amyloidogenic proteins are increasingly identified, and their treatment is protein-specific (Table 1). Clinical suspicion for amyloidosis in this particular case was very low in the absence of proteinuria and paraproteinaemia. The absence of proteinuria may reflect early glomerular involvement by amyloid, or potentially a feature of renal amyloidosis associated with this novel ALECT2. There is no specific therapy for this form of amyloidosis, and management is focused on secondary renal protective measures.

Conflict of interest statement. None declared.

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