The occurrence of renal amyloidosis and fibrillary glomerulonephritis in the same biopsy specimen is exceptional and poses a diagnostic challenge. We describe the case of a non-Hispanic White patient with end-stage kidney disease due to fibrillary glomerulonephritis who received a second living donor kidney from a Hispanic individual. A 40-month–posttransplantation biopsy performed for an elevated serum creatinine level revealed interstitial congophilic deposits and glomerular noncongophilic fibrillary deposits, in addition to rejection. Separate laser microdissections of the glomerular and interstitial deposits followed by liquid chromatography–tandem mass spectrometry (LC MS/MS) revealed DNAJB9 peptide spectra in glomeruli and a peptide profile consistent with leukocyte chemotactic factor 2 (ALECT2) amyloidosis in the interstitium. Based on these findings, a 2-week–posttransplantation biopsy was re-reviewed and analyzed using LC MS/MS, which revealed a peptide profile consistent with ALECT2 amyloidosis in the interstitium, without peptide spectra for ALECT2 or DNAJB9 in glomeruli. The findings were consistent with donor-derived ALECT2 amyloidosis and recurrent fibrillary glomerulonephritis. At 49 months posttransplantation, allograft function was stable with minimal proteinuria. Thus, LC MS/MS was crucial to establish the accurate diagnosis of these 2 nephropathies characterized by fibrillary deposits. The indolent posttransplantation course suggests that donated kidneys with focal interstitial ALECT2 deposits may be suitable for transplantation but the deposits persist for many years.

INTRODUCTION

Leukocyte chemotactic factor 2 (ALECT2) amyloidosis is a recently described form of amyloidosis1 that typically manifests as chronic decreased kidney function with bland urinary sediments,2,3 although postmortem analysis revealed consistent involvement of liver, spleen, lungs, and adrenal glands,4 usually subclinical. Contrary to other types of amyloidosis, it has a strong bias toward certain ethnic groups, including Hispanics of Mexican origin, Egyptians, and Punjabs, whereas it is very rare in non-Hispanic White populations.5,6,14 Pathogenesis is still unknown, but it could be due to leukocyte cell–derived chemotaxin 2 overexpression by hepatocytes.5,7 Overall survival is excellent due to the absence of heart involvement, whereas kidney survival is guarded although better than that of other types of amyloidosis.2,3,5,6 There is no known therapy, aside from kidney transplantation. ALECT2 amyloidosis has been only rarely described in the kidney allograft.3,9,10

Fibrillary glomerulonephritis (FGN) was historically defined by glomerular deposition of Congo red–negative, randomly oriented fibrils that stain with antiserum to immunoglobulin G (IgG),11,12 although recent series documented that some cases are Congo red–positive13,14 and/or IgG-negative.13 The fibrils of FGN resemble amyloid fibrils but are about twice as large, although there is a significant overlap and thus fibril diameter should not be solely relied on to make this distinction. The recent identification by laser microdissection–assisted liquid chromatography–tandem mass spectrometry (LC MS/MS) of DNAJB9 as a sensitive and specific marker for FGN has revolutionized the diagnosis of this disease16–18 and now allows for distinction from amyloidosis (including the distinction between congophilic FGN and amyloidosis)13,14 and other glomerulopathies characterized by organized deposits.16,17 As in ALECT2 amyloidosis, there is no effective treatment for FGN aside from kidney transplantation, which is associated with disease recurrence in some patients.14

Although the occurrence of 2 types of amyloidosis in the same patient has been reported,19 the presence of amyloidosis and FGN in the same kidney biopsy specimen has not been previously described to our knowledge. We describe an unusual case of donor-derived ALECT2 amyloidosis concurrent with recurrent FGN in the kidney allograft. Laser microdissection of separate anatomic sites of the kidney followed by LC MS/MS was crucial to establish the accurate diagnosis of these 2 nephropathies characterized by randomly oriented fibrillary deposits.

CASE REPORT

The patient was a non-Hispanic man in his early 50s with end-stage kidney disease secondary to Congo red–negative FGN (Fig 1A) who received a living-unrelated donor kidney transplant from a Hispanic man in his early 50s. The patient had a previous kidney transplant from his brother 7 years prior that was lost due to recurrent disease 6 years postimplantation. Pretransplantation evaluation of the second transplant revealed panel-reactive antibody values for HLA antigen class I of 8% and HLA antigen class II of 8%, a negative cross-match, and 3AB2DR HLA antigen.

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mismatches with the donor. His induction therapy consisted of thymoglobulin and methylprednisolone and his maintenance therapy consisted of tacrolimus and mycophenolate mofetil (steroid-free regimen).

Two weeks postimplantation, the patient’s serum creatinine level acutely increased from 2.3 on discharge to 5.5 mg/dL, which prompted a kidney biopsy that showed acute cellular rejection Banff grade 2A (without evidence of recurrent disease by electron microscopy), which was successfully treated with methylprednisolone and thymoglobulin. Random urinary protein-creatinine ratio was 540 mg/g.

Forty months posttransplantation, the patient was noted to have a serum creatinine level of 1.5 mg/dL, which was elevated above baseline. Urinalysis showed trace blood, and random urinary protein-creatinine ratio was 918 mg/g. There was no evidence of obstruction, tacrolimus level was within the therapeutic range, BK virus DNA was not detected in plasma using reverse transcriptase–polymerase chain reaction, and donor-specific antibody panel was negative. A kidney biopsy was performed.

The biopsy showed features of active antibody-mediated rejection with peritubular capillaritis (ptc3), mild glomerulitis (g1), and diffuse C4d positivity in peritubular capillaries (C4d3) and features suspicious for concurrent acute cellular rejection (Banff grade borderline: i1, t1, v0). There was mild mesangial expansion and hypercellularity (Fig 2A). Immunofluorescence revealed glomerular deposition of IgG (2+), IgM (trace), C3 (1+), C1q (1+), κ (1+), and λ (2+). On electron microscopy, randomly oriented straight fibrils measuring 15 nm in mean thickness were seen permeating the mesangial matrix and segmentally the glomerular basement membrane (Fig 1B), similar to the native kidney biopsy (Fig 1A). In addition, smaller (10 nm in mean thickness) randomly oriented straight fibrils were seen permeating the cortical interstitium (Fig 1C). Congo red stain was negative in glomeruli but was positive in the interstitium, with anomalous colors under polarized light (Fig 2B and C).

To further characterize the glomerular and interstitial deposits, we performed separate laser microdissections of the Congo red–negative glomerular deposits and the Congo red–positive interstitial deposits, followed by LC MS/MS. In glomeruli, abundant peptide spectra corresponding to DNAJB9 were detected, consistent with recurrent FGN, without the peptide profile of amyloidosis (Fig 3). In contrast, in the congophilic interstitial deposits, a peptide profile consistent with ALECT2 was detected without spectra for DNAJB9 (Fig 3). Based on these findings, the paraffin block of the 2-week posttransplantation biopsy was obtained, and sections were stained with Congo red and analyzed using LC MS/MS. Patchy Congo red–positive amyloid deposits were seen in the interstitium, which by LC MS/MS exhibited a peptide profile...
Figure 2. Light microscopy findings in the biopsy of the second allograft. (A) The glomerulus shown exhibits mild global mesangial hypercellularity and matrix expansion (periodic acid–Schiff stain). (B) Interstitial and tubular basement membrane congophilic amyloid deposits. (C) The congophilic deposits show anomalous colors (so called “apple green birefringence”) under polarized light (A–C: original magnification, ×400).

Figure 3. Proteomics identifies ALECT2 (leukocyte chemotactic factor 2)-type amyloidosis and fibrillary glomerulonephritis biomarkers in different anatomic compartments in the patient’s renal biopsy: separate laser microdissections followed by liquid chromatography–tandem mass spectrometry (LC MS/MS) were performed on Congo red–positive interstitial deposits and Congo red–negative glomeruli. The protein identification profile from all samples is shown. Numbers in green boxes show the total number of MS/MS spectral counts associated with each protein in the corresponding sample. MS/MS spectral counts are a surrogate measure of protein abundance in the sample.21 Proteins with MS/MS counts of 5 or higher are considered for clinical interpretation, and at least 2 universal amyloid tissue biomarkers must be present to verify a diagnosis of amyloidosis. The interstitial deposits (columns 1 and 2) contain the universal amyloid tissue biomarkers apolipoprotein E (APOE) and serum amyloid P-component (SAMP), as well as LECT2 protein, which is the type-defining marker for ALECT2-type amyloid. The glomerular deposits (column 3) lack the proteomic features of amyloidosis but instead contain abundant spectral counts for DNAJB9, which is a biomarker for fibrillary glomerulonephritis.
consistent with ALECT2. No spectra for DNAJB9 or a peptide profile of ALECT2 were detected in glomeruli.

The patient was treated with methylprednisolone, plasmapheresis, and intravenous immunoglobulin, followed by prednisone taper. Nine months later (49 months posttransplantation), serum creatinine level was 1.56 mg/dL and random urinary protein-creatinine ratio was 658 mg/g. The donor’s most recent serum creatinine level and random urinary protein-creatinine ratio, 51 months postdonation, are 1.31 mg/dL and 141 mg/g, respectively.

**DISCUSSION**

The incidence of ALECT2 amyloidosis in kidney allograft biopsies has not been investigated. Anecdotal reports showed that it can be of donor origin\(^1\),\(^9\) or de novo.\(^10\) Recurrence of renal ALECT2 amyloidosis is questionable. In our previous report of 72 patients with ALECT2 amyloidosis, 5 received a kidney transplant.\(^3\) In one of the patients who received a living related donor kidney from his niece, amyloid deposits were detected on a 6-month posttransplantation biopsy, which we interpreted as evidence of disease recurrence.\(^3\) However, several years later, the donor’s father (ie, recipient brother) had renal ALECT2 amyloidosis diagnosed. Thus, retrospectively, that case likely represents familial donor-derived (rather than recurrent) ALECT2 amyloidosis (S.H.N., unpublished data).

In the current case, a non-Hispanic White patient received a kidney from a Hispanic individual and a 2-week posttransplantation biopsy revealed interstitial ALECT2 amyloidosis; thus, ALECT2 is likely donor derived. The recipient’s ethnicity and short time from implantation to amyloid detection argue against de novo disease and the absence of ALECT2 in the native biopsy and first allograft argue against recurrent disease. However, the patient had recurrent FGN involving glomeruli but not the interstitium. In a series from our center of 14 patients with FGN who underwent kidney transplantation and protocol allograft biopsies (which included the current case), only 3 (21%) had histologic evidence of recurrence, detected 5 to 10 years posttransplantation, and was associated with an indolent course.\(^2\) Interestingly, our patient who lost his first allograft due to recurrent FGN had stable second-allograft function more than 4 years postimplantation with only minimal proteinuria, despite having FGN, ALECT2 amyloidosis, and rejection. Thus, both donor-derived ALECT2 amyloidosis and recurrent FGN in the second allograft could be subclinical.

The exceptional development of amyloidosis and FGN in the same biopsy specimen poses a diagnostic challenge to the pathologist due to the ultrastructural similarities of these diseases and the fact that deposits in some FGN cases are Congo red-positive\(^3\),\(^14\) and/or IgG-negative.\(^15\) Separate laser microdissections of glomerular and interstitial deposits followed by LC MS/MS were crucial to establish the accurate diagnosis of these 2 nephropathies. However, this technique is not widely available. Alternatively, the combination of DNAJB9 and LECT2 immunohistochemical stains could be used to establish the diagnosis. The indolent posttransplantation course supports that donated kidneys with focal ALECT2 deposits may be suitable for transplantation but the deposits in the allograft persist for many years. The impact of kidney donation in individuals with subclinical ALECT2 amyloidosis remains to be determined.

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