

Evidence for Transition From Light Chain Deposition Disease by Immunofluorescence-Only to Classic Light Chain Deposition Disease



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INTRODUCTION

Light chain deposition disease (LCDD) is a rare disease associated with monoclonal gammopathy of renal significance (MGRS) or multiple myeloma.^{1,2} Kidney involvement is nearly universal and recurrence is frequent if the MGRS is not treated before kidney transplantation (KTx).^{2–4} The monoclonal immunoglobulin (Ig) light chain (LC) is deposited in a nonfibrillar, Congo-red–negative pattern.⁵ Diagnosis requires demonstration of diffuse linear LC staining in the basement membranes of glomeruli, tubules, and vascular myocytes on immunofluorescence (IF) and corresponding finely granular, punctate (“powdery”) electron dense deposits ultrastructurally (LCDD IF/electron microscopy [EM]).^{2,5,6} Approximately two-thirds of cases also have nodular mesangial sclerosis. Cases of LCDD by IF only (LCDD-IF) without EM deposits have been reported particularly when associated with concurrent myeloma cast nephropathy.^{6–8} Whether this finding is secondary to nonpathogenic trapping of circulating LCs that do not form true deposits, insufficient aggregation of deposits not visualized by EM, or the possibility that not all LCs form electron-dense deposits have been proposed but none are substantiated.^{6–9, S1} Even more important is the debate whether these patients require treatment if myeloma cast nephropathy is not present. Here, we document a transition in three allografts from LCDD-IF to LCDD IF/EM, and thus we propose that LCDD-IF could represent an early stage of the disease.

CASE PRESENTATION

Methods

Three patients with LCDD in the renal allograft in whom sequential protocol and/or indication biopsy specimens showed transition from LCDD-IF to classic LCDD (LCDD IF/EM) were identified from the renal pathology archives at Mayo Clinic. Two patients were transplanted and followed at Mayo Clinic, Rochester, Minnesota, USA, where protocol transplant biopsy specimens are generally performed at implantation, 3 to 4 months, and at 1, 2, and 5 years. The third patient was transplanted elsewhere. Clinical data, treatment, and follow-up were obtained from the patients’ electronic medical records.

A total of 20 kidney allograft biopsies were performed on these three patients (each with ≥ 4 biopsies performed). Most biopsy specimens were analyzed by light microscopy (LM), IF, and EM. For LM, cases were stained with hematoxylin and eosin, periodic acid–Schiff, Masson’s trichrome, and Jones methenamine silver. For immunofluorescence, 3- μ m cryostat sections were stained with polyclonal fluorescein isothiocyanate-conjugated antibodies to immunoglobulin G (IgG), IgM, IgA, C3, C1q, C4d, kappa, lambda, fibrinogen, and albumin.

Case histories

Case 1

A 56-year-old male underwent KTx for presumed chronic interstitial nephritis (Table 1, Table S1). Elevation of serum creatinine to 133 mmol/l without

Table 1. Clinical characteristics at LCDD-IF and LCDD IF/EM

	Allograft #				
	1	2.1	2.2	3	3R
LCDD-IF					
Time of MGRS detection	4 months post-KTx	1 month pre-KTx	74 months pre-KTx	16 months pre-KTx	
Time from KTx to LCDD-IF, months	7	25	25	3	66
Time from MGRS detection to LCDD-IF, months	3	26	99	19	82
Kidney biopsy	Indicated	Protocol	Protocol	Protocol	
Serum creatinine, mmol/l	150	133	97	97	106
κ FLC (3.3 to 19.4 mg/l)	163	130	45.7	856	458
K:λ FLC ratio	23.7	12.3	5.47	334.38	23.1
Serum IFN	negative	IgGκ	IgGκ	κ	negative
Serum M-spike, g/l	negative	10	9	Not measurable	Not measurable
Hematuria	no	no	no	no	no
Urine IFN	κ	κ	κ	κ	κ
Proteinuria, mg/d	513	53	96	876	69
Urine M-spike, mg/d	165	Not measurable	Not measurable	150	Not measurable
Bone marrow monoclonal plasma cells, %	5 to 10	7	5	7	Not performed
LCDD IF/EM					
Time from LCDD-IF to LCDD IF/EM, months	13	26	No progression	No progression	41
Kidney biopsy	Indicated	Protocol			Indicated
Serum creatinine, mmol/l	177	168			186
κ FLC (3.3 to 1.49 mg/l)	187	154			1680
K:λ FLC ratio	20.8	12.9			53.3
Serum IFN	Negative	IgGκ			Negative
Serum M-spike, g/dl	Not detected	1.3			Negative
Hematuria	Yes	No			No
Urine IFN	κ	κ			κ
Proteinuria, mg/d	2497	64			32
Urine M-spike	389	Not measurable			Not measurable
Bone marrow plasma monoclonal cells, %	5 to 10	7			10

FLC, free light chain; IFN, immunofixation; IgG, immunoglobulin G; KTx, kidney transplantation; LCDD-IF, light chain deposition disease by immunofluorescence only; LCDD IF/EM, light chain deposition by immunofluorescence and electron microscopy; MGRS, monoclonal gammopathy of renal significance.

proteinuria prompted a kidney biopsy 1 month post-KTx which showed acute tubular injury with negative IF. Further evaluation revealed an elevated kappa free light chain (FLC). Another biopsy 7 months post-KTx was performed because of increased serum creatinine at 150 mmol/l and mild proteinuria at 513 mg/d showed LCDD-IF (allograft 1). The patient was observed and at 20 months post-transplantation the serum creatinine level increased to 177 mmol/l with 2.5 g/d of proteinuria. Repeat biopsy showed LCDD IF/EM. Bone marrow biopsy showed 5% to 10% monoclonal plasma cells. The patient achieved a complete response with cyclophosphamide/bortezomib/dexamethasone resulting in improvement of creatinine and normalization of proteinuria.

Case 2

A 60-year-old female underwent KTx (allograft 2.1) for presumed analgesic nephropathy; she was found to have LCDD-IF on a protocol allograft biopsy 25 months post-KTx. A monoclonal IgGκ was identified 1 month pretransplantation and was believed to be a monoclonal gammopathy of undetermined significance (Figure 1a). Protocol biopsy at 51 months showed LCDD IF/EM. A

third biopsy performed 63 months post-transplantation showed persistent LCDD IF/EM with progression to nodular mesangial sclerosis. Proteinuria had increased to 0.9 g/d and creatinine increased to 168 mmol/l. Bone marrow biopsy showed 7% monoclonal plasma cells and bortezomib was started but discontinued after 2.25 cycles due to painful peripheral neuropathy. With declining kidney function, she underwent a pre-emptive second KTx (allograft 2.2) 73 months after the first KTx. LCDD-IF was identified 25 months after the second KTx along with progression of κ FLC. Treatment with ixazomib/dexamethasone resulted in a 91% reduction of the κ FLC and the deposits seen on IF disappeared 3 years after starting therapy. Her last recorded creatinine level was 118 mmol/l and she had no proteinuria.

Case #3

A 56-year-old female underwent a KTx for LCDD before a planned autologous stem-cell transplantation. LCDD-IF was shown on the 3-month surveillance biopsy specimen. The patient achieved a very good partial response and the LC deposits disappeared on a protocol biopsy specimen 2 years later. Thirty-five

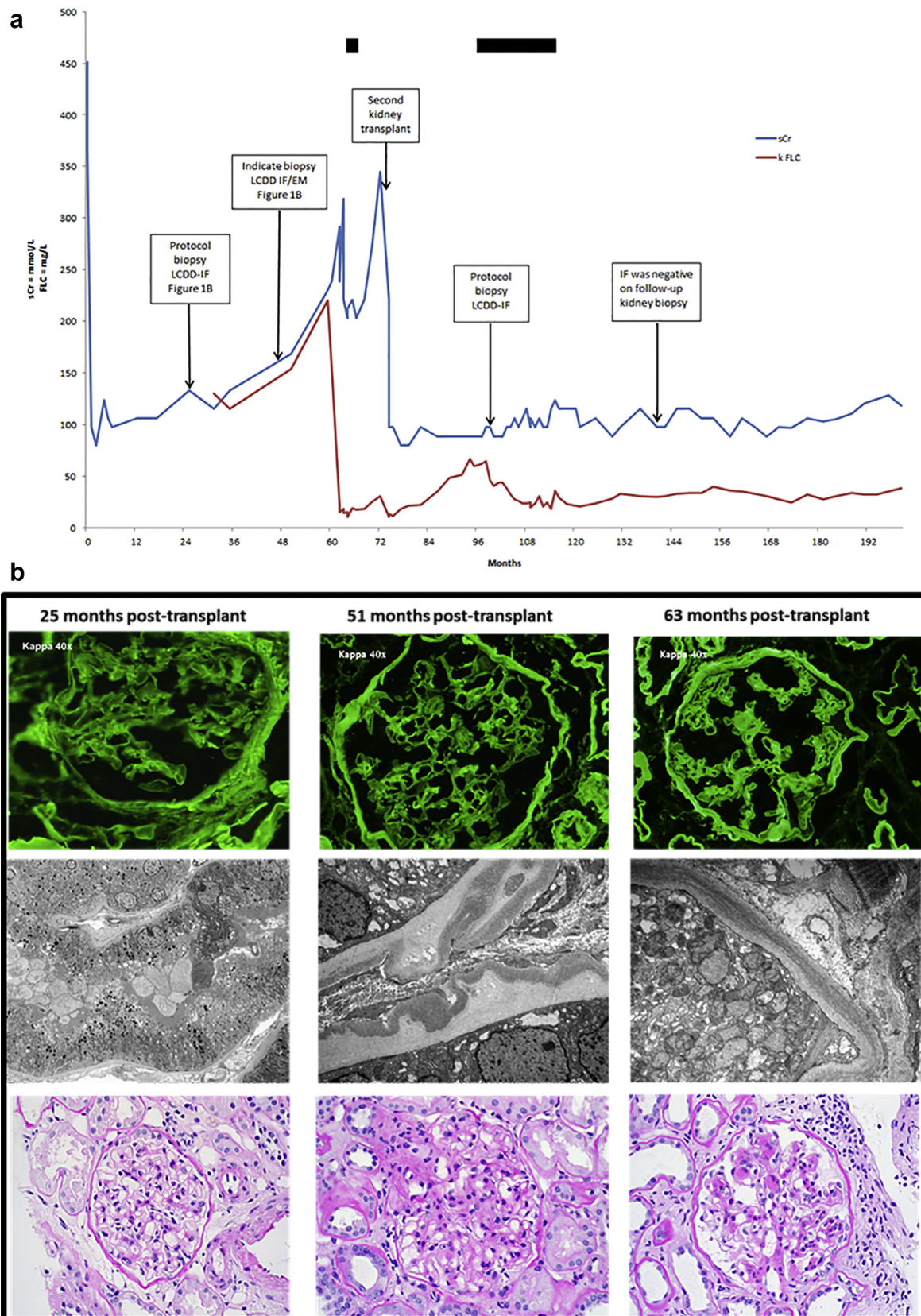


Figure 1. Patient 2. (a) Clinical course of patient 2 which includes allografts 2.1 and 2.2. Serum creatinine (sCr) and κ free light chain (κ FLC) from the time of kidney transplantation of allograft 2.1 in months. Arrows indicate allograft biopsy specimens showing light chain deposition disease by immunofluorescence only (LCDD-IF) and LCDD by immunofluorescence and electron microscopy (LCDD IF/EM). Black bars represent treatment with clone-directed therapy. (b) Pathologic findings in patient 2. A biopsy performed 25 months post-transplantation revealed bright linear staining of glomerular and tubular basement membranes for kappa light chain on IF (upper left image), no punctate deposits along glomerular or tubular basement on EM (middle left), and normal-appearing glomeruli on light (continued)

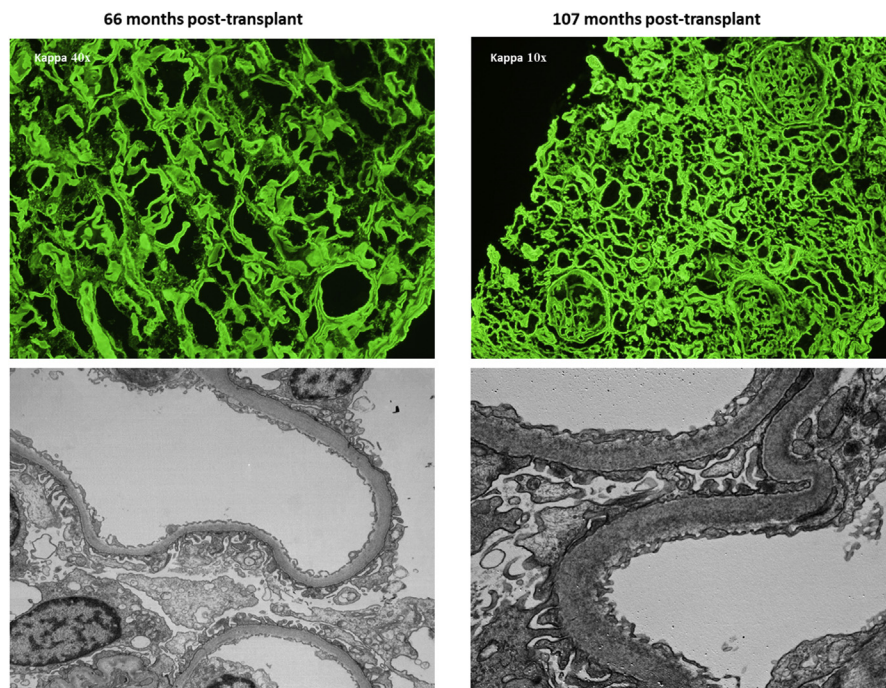


Figure 2. Pathologic findings in patient 3. An allograft biopsy performed 66 months post-transplantation revealed bright linear staining of glomerular and tubular basement membranes for kappa light chain on immunofluorescence (IF) (upper left image) with no punctate deposits along glomerular (lower left) or tubular basement membranes on electron microscopy (EM). A repeat biopsy 107 months post-transplantation similarly revealed bright linear staining of glomerular and tubular basement membranes for kappa light chain on IF (upper right), but punctate “powdery” electron dense deposits were seen along glomerular (lower right) and tubular basement membranes on EM.

months post-KTx, melphalan and dexamethasone were started for 6 months for increasing κ FLC without proteinuria. LCDD-IF returned 66 months post-KTx. Lenalidomide was attempted but she did not tolerate it. LCDD-IF progressed to LCDD IF/EM (Figure 2) (allograft 3R) 41 months after the relapse. Melphalan and dexamethasone followed by cyclophosphamide/bortezomib/dexamethasone achieved a complete hematologic response. Although she never developed proteinuria, the last creatinine had risen to 256 mmol/l.

RESULTS

The demographics and transplant characteristics are listed in Table S1. The median time from transplant to LCDD-IF was 7 months (range, 3 to 25 months) (Table 1). One patient had biopsy-proven LCDD in the native kidney whereas native kidney biopsy was not performed in the other two patients. All three patients had evidence of a monoclonal gammopathy—detected pre-KTx or soon

after. No patient received clone-directed therapy before kidney transplantation. The monoclonal gammopathy was initially MGRS in all three patients but evolved into symptomatic myeloma 20 to 59 months post-KTx in two patients. Median time from LCDD-IF to LCDD IF/EM was 26 (range, 13 to 41) months. At the time of LCDD IF/EM, all patients had elevated creatinine from baseline and one had proteinuria (Table 1).

The pathologic findings are detailed in Table S2. On LM, LCDD-IF was associated with unremarkable glomeruli and no or minimal (<10%) interstitial fibrosis/tubular atrophy. One showed acute tubular injury, two showed mild focal thickening of tubular basement membranes (BMs), and none showed thickening of vascular myocyte BMs. IF revealed bright (2 to 3+) linear staining of tubular BMs (three patients) and glomerular BMs (two patients) for κ with negative λ . No punctate deposits were seen along glomerular or tubular BMs on EM (Figure 1b and Figure 2). LM of LCDD IF/EM revealed normal glomeruli in one patient

Figure 1. (continued) microscopy (LM) (lower left). A repeat biopsy 51 months post-transplantation similarly revealed bright linear staining of glomerular and tubular basement membranes for kappa light chain on IF (upper center), but punctate “powdery” electron dense deposits were seen along tubular (middle center) and glomerular basement membranes on EM, and mild mesangial sclerosis was seen on LM (lower center). A repeat biopsy performed 63 months post-transplantation similarly revealed bright linear staining of glomerular and tubular basement membranes for kappa light chain on IF (upper right) and punctate powdery electron dense deposits were seen along tubular (middle right) and glomerular basement membranes on EM, but the glomerular pattern of injury on LM evolved into nodular glomerulosclerosis (lower right).

Table 2. Teaching points

1 We present three cases of LCDD-IF in the renal allograft which progressed to LCDD IF/EM when left untreated, suggesting that this lesion could be an early lesion of LCDD.
2 Surveillance biopsies should be performed in patients with high risk of relapse in the kidney allograft.
3 Treatment of LCDD-IF should be considered as delayed treatment could lead to graft loss.

EM, electron microscopy; IF, immunofluorescence; LCDD, light chain deposition disease.

and minimal to mild mesangial sclerosis in 2 patients, with less than 15% interstitial fibrosis/tubular atrophy. One patient showed acute tubular injury and two patients showed thickening of tubular and vascular myocyte BMs. IF revealed 2 to 3+ linear staining of tubular and glomerular BMs for κ with negative λ in all. On EM, punctate electron dense deposits were seen along tubular BMs in all three patients, along glomerular BMs in 2 patients, and in the mesangium in one patient. Patient 2 who had mild mesangial sclerosis underwent a repeat biopsy 1 year later which revealed progression to nodular glomerulosclerosis (Figure 1b).

The median post-transplantation follow-up time was 9.7 years (range, 5.0 to 16.5 years). Various treatments were used for MGRS and multiple myeloma with variable outcomes (Table S3). One allograft which had developed mesangial sclerosis was lost despite achievement of very good partial response. Two allografts were functioning with stable creatinine and no proteinuria.

DISCUSSION

In this study, we provide evidence that LCDD-IF could represent an early LCDD lesion in the allograft (Table 2). In all allografts, LCDD-IF was detected before alterations in baseline serum creatinine or proteinuria. Left untreated, the allografts with LCDD-IF progressed to LCDD IF/EM within 1 to 3 years accompanied by increasing serum creatinine, proteinuria, or both. Focal thickening of the tubular and vascular myocyte BMs, and minimal mesangial sclerosis appear to be the earliest LM manifestations, whereas nodular glomerulosclerosis occurs at a later stage matching the animal model of LCDD.^{S2} The evolution from IF-only deposits to deposits by IF and EM is analogous to very early recurrent membranous nephropathy.^{S3} The detection of the LCDD-IF would be impossible without surveillance biopsies as clinical manifestations were absent at the time of the biopsy. Demonstration of the progression from LCDD-IF to LCDD IF/EM is difficult to show in the native kidney as repeat native biopsies are not typically performed in LCDD and because native kidney LCDD-IF is often diagnosed simultaneously with myeloma cast nephropathy which requires immediate

treatment. Our findings, however, may not be true for all patients with LCDD-IF as the three patients we describe might represent a subset of LCDD-IF patients who have the “right” LC physicochemical properties to allow for recurrence in the allograft and progression to LCDD IF/EM.

The recognition of LCDD-IF as an early lesion has important clinical implication in renal allografts because LCDD frequently recurs after KTx and graft loss occurs despite the use of clone-directed therapy.^{3,4} Early treatment may be vital for graft preservation as the kidney function was preserved and the LC deposits actually disappeared on subsequent biopsy specimens in two allografts (2.2 and 3) when treatment was initiated at the LCDD-IF stage. In contrast, one graft with nodular mesangial sclerosis (2.1) was lost and another (3R) sustained substantial decline in kidney function despite achieving good hematologic response when treatment was delayed until development of LCDD IF/EM.

CONCLUSION

Our study suggests that LCDD-IF could be an early lesion of LCDD in the kidney allograft. Protocol biopsies and early initiation of treatment should be considered as delayed treatment could lead to graft loss.

DISCLOSURES

The study was approved by the Institutional Review Board of Mayo Clinic Foundation IRB #19-005012. All the authors declare no competing interests.

PATIENT CONSENT

Consent was received from the patient.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Demographics and transplant characteristics.

Table S2. Pathologic findings.

Table S3. Treatment and outcomes.

Supplemental References.

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