

Case Report

Recurrent light and heavy chain deposition disease after renal transplantation

Bassam Alchi¹, Shinichi Nishi², Seitaro Iguchi¹, Masaaki Shimotori¹, Minoru Sakatsume¹, Mitsuhiro Ueno¹, Ichiei Narita¹, Kazuhide Saito³, Kota Takahashi³ and Fumitake Gejyo¹

¹Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, ²Blood Purification Center, Niigata University Hospital, Japan and

³Division of Urology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

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Introduction

Light and heavy chain deposition disease (LHCDD) is a rare entity with less than two dozen reported cases [1,2]. The term LHCDD was proposed in 1984 as a variant of light chain deposition disease (LCDD), to characterize a subset of patients in whom deposits contain both light and heavy chain antigenic determinants.

We present a case of LHCDD in a renal graft and evidence that this process represented disease recurrence. This case illustrates how difficult LHCDD can be to diagnose. The patient's post-transplant course suggests that LHCDD may recur in transplanted kidneys, and may evolve into multiple myeloma and AL-amyloidosis.

Case

A 51-year-old Japanese man was admitted to our institution in February 1996 for renal transplantation. He had first presented to an outside hospital in February 1987 with asymptomatic proteinuria and haematuria. At that time, his urinary protein excretion was 1.2 g/day, urinary red cell count 7 per high power field, and serum creatinine 100 µmol/l, and his creatinine clearance was estimated to be 1.16 ml/s/1.73 m² body surface area (BSA). His total serum protein was 50.6 g/l, γ-globulin 7.1%, immunoglobulin G (IgG)

4.6 g/l [normal range (NR), 8.7–17.0 g/l], IgA 1.68 g/l (NR, 1.1–4.1 g/l), and IgM 2.82 g/l (NR, 0.65–1.35 g/l) without a monoclonal component. The C3, C4 and CH50 levels were 430 mg/l (NR, 650–1350 mg/l), 130 mg/l (NR, 130–350 mg/l) and 22 U/ml (NR, 28–53 U/ml), respectively. His renal biopsy (Figure 1A) showed nodular mesangial matrix expansion with mild mesangial hypercellularity. The nodular lesions stained positive with periodic acid-Schiff, but when stained with Congo-red, no amyloid substance was detected in those lesions viewed in polarized light. Immunofluorescence studies showed coarse staining for IgG, C3 and C1q in the mesangium, and linear staining for IgG, along the GBM, tubular basement membrane (TBM), Bowman's capsule and vessel walls, and for C1q, along the TBM. On electronmicroscopy, homogeneously dense deposits were observed in the GBM (Figure 1B). Based on these findings, the diagnosis of type II membranoproliferative glomerulonephritis (nodular type) was made, but since the presence of C3 nephritic factor was not confirmed, the diagnosis was reviewed 10 years later. The patient was treated initially with prednisolone 20 mg/day, cyclophosphamide 50 mg/day and dipyridamole 300 mg/day for 9 months but without clinical improvement. In February 1995, regular haemodialysis was begun because he developed end-stage renal failure.

In February 1996, the patient received renal transplantation from his fully HLA-matched younger brother. Pre-transplant biopsy of the donor and 1 h post-transplant graft biopsy showed almost normal findings on light, immunofluorescence and electron microscopy. On the eighth post-operative day, the patient showed signs of acute rejection, and was treated with intravenous methylprednisolone 500 mg daily for 3 days and antilymphocyte globulin 1 g daily for 10 days. Because of his continued hypogammaglobulinaemia and unexplained anaemia, a bone marrow aspirate was done 1 month later, and appeared to be

Correspondence and offprint requests to: Bassam Alchi, 1-757 Asahimachi-dori, Niigata 951-8510, Japan. Tel: +81 25 227 2200; Fax: +81 25 227 0775; Email: bassamalchi@hotmail.com

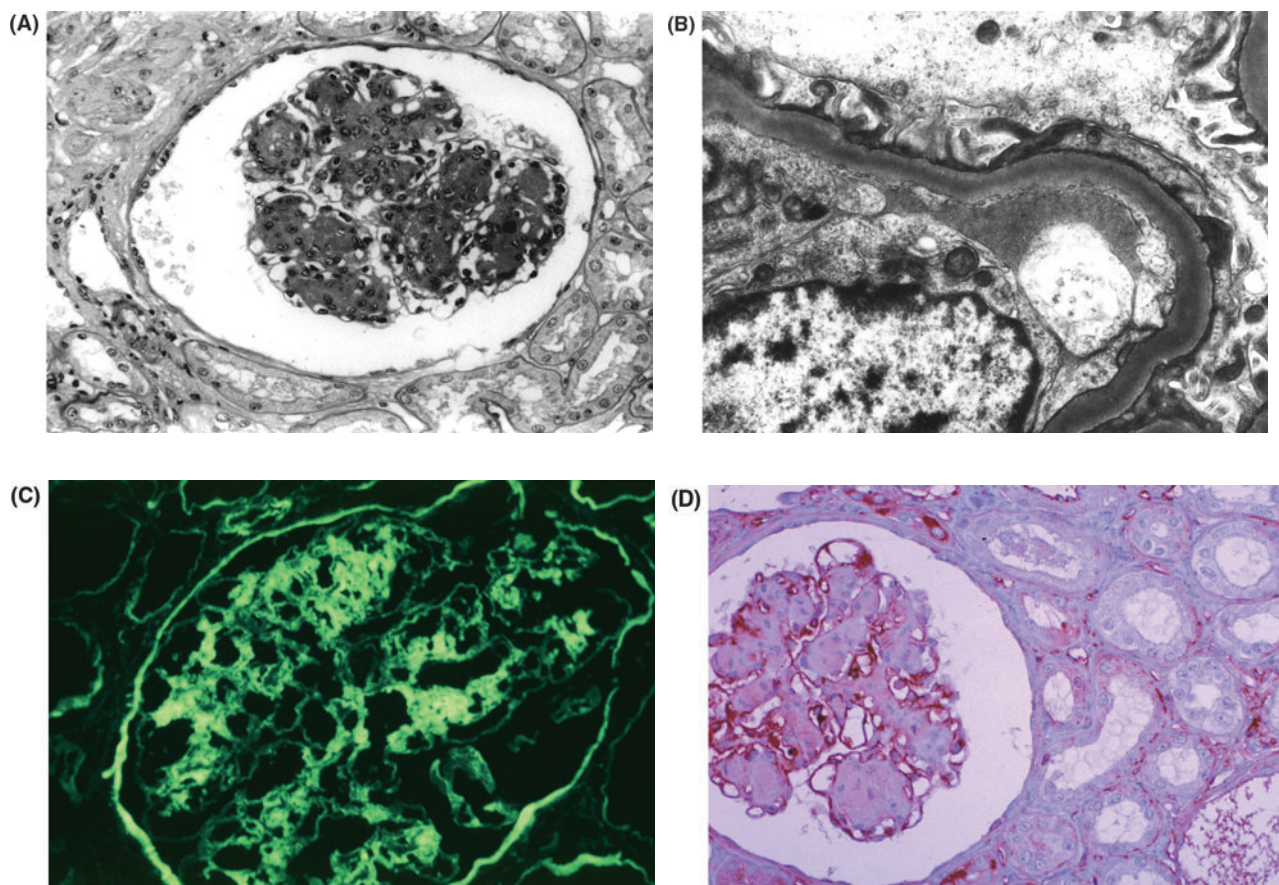


Fig. 1. Photomicrographs of biopsies from the patient's native kidney. (A) Light microscopy of a representative glomerulus shows nodules positively stained with periodic acid-Schiff (PAS) in the mesangial area, associated with mesangial hypercellularity (original magnification $\times 100$). (B) Electronmicrograph shows homogenous electron-dense deposits in the glomerular basement membrane (original magnification $\times 10\,000$). (C) Immunofluorescence microscopy for λ -light chain displays homogenous deposition in mesangial nodules, and linear deposition along glomerular basement membranes, Bowman's capsule, and tubular basement membranes (original magnification $\times 200$). (D) Paraffin section stained with a polyclonal γ -chain antibody conjugated with peroxidase. The dark-brown reaction product is shown deposited in glomerular and tubular basement membranes (original magnification $\times 100$).

normal. However, bone marrow plasma cells were not examined at that time by immunoperoxidase staining to determine if monoclonality was present. When the patient was discharged, his serum creatinine was $117\ \mu\text{mol/l}$, and he was on the following immunosuppressive medications: cyclosporine $4\ \text{mg/kg}$ of body weight; mizoribine, a purine synthesis inhibitor used mainly in Japan [3], $200\ \text{mg/day}$; and methylprednisolone $8\ \text{mg/day}$.

In July 1997, the patient underwent graft biopsy because his proteinuria had increased to $1\ \text{g/day}$. Serum creatinine was $133\ \mu\text{mol/l}$ and creatinine clearance $0.66\ \text{ml/s/1.73 m}^2\ \text{BSA}$. Serum total protein was $50\ \text{g/l}$ and γ -globulin 8.3% . Serum immunoelectrophoresis showed worsening hypogammaglobulinaemia (IgG $1.92\ \text{g/l}$, IgA $0.5\ \text{g/l}$ and IgM $0.55\ \text{g/l}$), but not a monoclonal band. Hypocomplementaemia continued after transplantation, with C3, C4 and CH50 at $390\ \text{mg/l}$, $160\ \text{mg/l}$ and $8\ \text{U/ml}$, respectively. Light microscopic examination of the graft biopsy showed a mild increase of the mesangial matrix and, in one glomerulus, a nodular lesion (Figure 2A). There was

no evidence of acute rejection. Immunofluorescence examination disclosed findings similar to those seen in the patient's native kidney, in addition to the linear deposition of λ -light chain along TBM, GBM, Bowman's capsule and vessel walls. Staining for κ -light chain was negative, as was Congo red staining. A search for monoclonal proteins containing heavy chains was undertaken, because of the hypocomplementaemia and the presence of C3 and C1q deposits in the kidney. Indirect immunofluorescence using mouse monoclonal antibodies specific for human γ chain subtypes 1 to 4 (SouthernBiotech, Birmingham, AL, USA) showed positive staining for $\gamma 1$ only in the same locations as IgG, whereas $\gamma 2$, $\gamma 3$ and $\gamma 4$ were not detected (Figure 2B). Double immunofluorescence for λ -light and $\gamma 1$ -heavy chains showed partial, rather than complete, co-localization (Figure 2C). Electron microscopy revealed dense subendothelial deposits along the inner aspect of the GBM (Figure 2D). Taken together, these findings confirmed the diagnosis of LHCDD (1).

The original pathology of the native kidney was re-evaluated retrospectively. Immunohistochemical

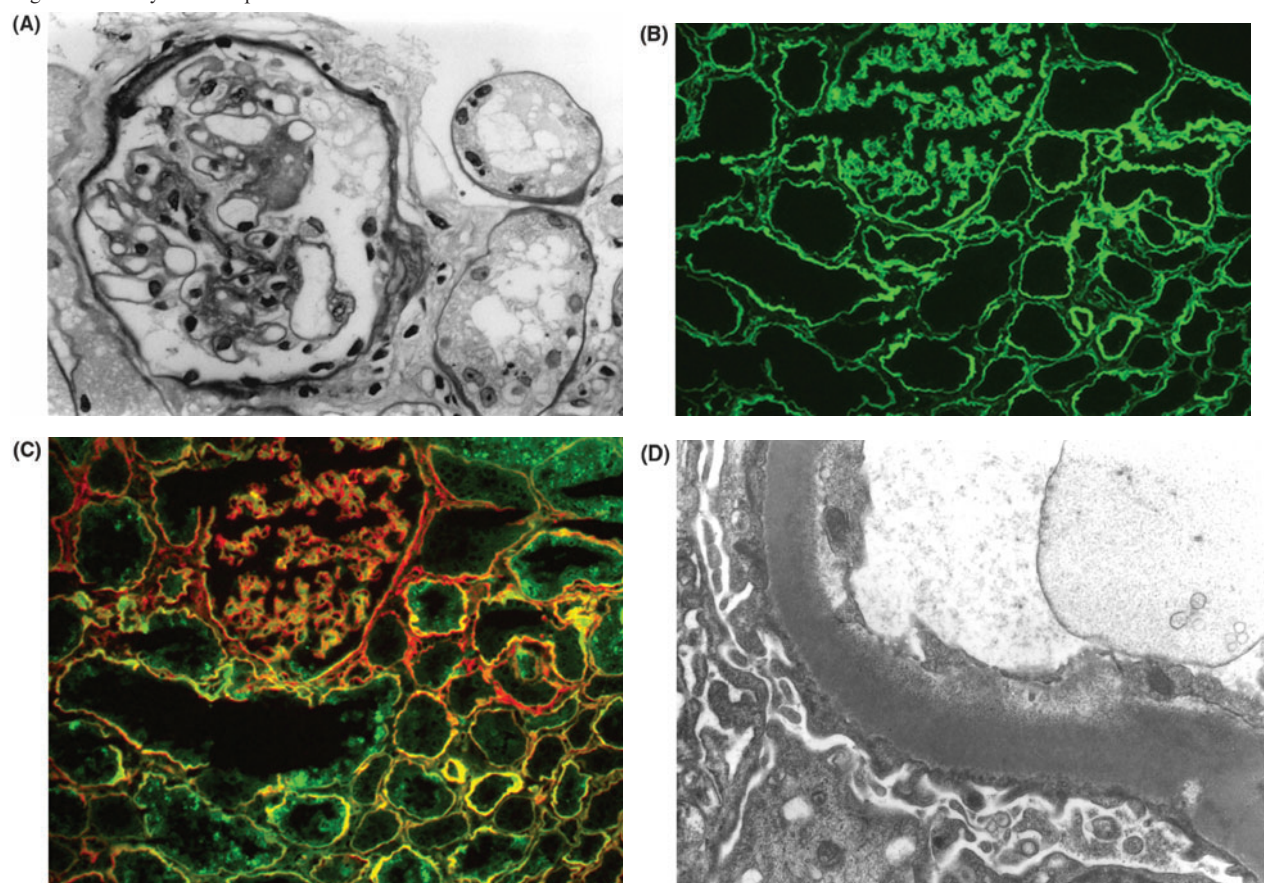


Fig. 2. Photomicrographs from the grafted kidney. (A) Light microscopy showing mild increase of mesangial matrix with a nodular lesion (original magnification $\times 100$). (B) Direct immunofluorescence showing linear staining for IgG along glomerular and tubular basement membranes, Bowman's capsule and vessel walls in the same locations as $\gamma 1$ (Figure 2C). (C) Double-immunofluorescence using a fluorescein isothiocyanate-labelled λ -light chain antibody and a monoclonal mouse anti-human $\gamma 1$ -heavy chain antibody followed by a rhodamine-labelled anti-mouse antibody. λ -Light chain (green) and γ -heavy chain (red) shows only partial colocalization (yellow) (original magnification $\times 200$). (D) Electronmicrograph shows dense subendothelial deposits along the endothelial aspect of basement membrane (original magnification $\times 10\,000$).

studies with antisera to human λ - and κ -light chains and with a polyclonal γ -heavy chain antibody (DAKO, Glostrup, Denmark) were performed on paraffin sections (since there was an inadequate amount of frozen material), and showed linear deposits of λ -light chain (Figure 1C) and γ -heavy chain (Figure 1D) along GBM, TBM and Bowman's capsule, but no deposits of κ -light chain.

In August 1998, the patient developed leg edema, ascites and purpura. Blood tests revealed mild anaemia with thrombocytopenia. The total serum protein was 46 g/l, proteinuria 1.1 g/day. Serum and urinary protein electrophoresis identified a monoclonal IgG λ paraprotein with free λ -light chains; bone marrow aspiration showed increased plasmacytosis (19.2%) with atypical plasma cells. Accordingly, we diagnosed multiple myeloma, and started treatments with melphalan 4 mg plus prednisolone 40 mg/day, for 4 days per course. A total of 10 courses of chemotherapy were administered over 3 years, without achieving complete remission; however, serum and urinary free λ -light chain were controlled at mean levels of 650 mg/l

(NR, 5.7–26.3 mg/l) and 450 mg/l (NR, <17 mg/l), respectively, and a repeat bone marrow aspiration showed marked reduction of the plasma cell count, to 4%.

The graft's function further deteriorated, and the patient had to return to regular haemodialysis in September 2002. Six months later, he presented with trismus and dysphagia. Extensive work-up to find the cause of trismus was negative, except for scleromyxoedema of the skin of the cheeks and neck. A biopsy from those skin lesions showed an eosinophilic material, identified as amyloid by staining with direct fast scarlet stain. Immunofluorescence studies on frozen sections of the skin were positive for λ -light chain, but they were negative for κ -light chain, AA protein and B_2 microglobulin. Electronmicroscopy revealed randomly oriented fibrils typical of AL-amyloidosis. The patient's condition gradually deteriorated until he died in October 2003 because of sepsis and malnutrition. No postmortem examinations were performed.

Discussion

Monoclonal immunoglobulin deposition diseases (MIDD), including LHCDD, can be suspected in any patient with proteinuria, nodular glomerulopathy and a monoclonal protein in serum or urine. However, in as many as 20% of patients with documented MIDD, a monoclonal protein is not detected (even with the use of most sensitive laboratory techniques), making the diagnosis more difficult [4]. This is because these monoclonal proteins may be detectable only intermittently or that they are found in serum and/or urine only in low concentrations [5]. Additionally, the overproduction of an abnormally structured immunoglobulin, which is rapidly degraded after secretion, may play a role in tissue deposition [6]. Our patient showed no evidence of a monoclonal band in serum or urine until towards the end of his clinical course. On the other hand, hypogammaglobulinaemia was the only sign of B-cell proliferative disorder in him, which suggests that hypogammaglobulinaemia should signify the presence of some form of MIDD in a patient with proteinuria (although the same combination is also seen in AL-amyloidosis).

The diagnosis of MIDD cannot be established by a simple histological examination. It requires immunofluorescence and the use of antisera specific for the individual light and heavy chains. In our patient, the diagnosis of LHCDD was overlooked before transplantation because of the following. First, in the past, the sera against light chain determinants were not routinely used in immunofluorescence studies of kidney biopsy specimens. The linear immunofluorescence staining with anti-IgG and anti-C1q sera along the TBM, which would have been very unusual in immune complex disease, should have triggered the suspicion that the underlying cause of the nephropathy of our patient was the systemic deposition of immunoglobulin fragments. Secondly, on electronmicroscopy the deposits were not typically granular or crystalline, but were homogenous, resembling those in immune complex diseases. Similar findings in rare cases of LHCDD have been reported [4]. Thirdly, hypocomplementaemia was consistent with the diagnosis of membranoproliferative glomerulonephritis; however, it is also a well-known feature of HCDD, specifically of the variants caused by γ 1- or γ 3-HCDD [7].

Although both monotypic light and heavy chains were found in this case, their only-partial co-localization in the kidney (Figure 2C) suggests that light and heavy chains precipitate separately, as independent subunits, rather than as a whole immunoglobulin molecule or they were differentially degraded and removed from the tissue after deposition.

Most patients with MIDD are not candidates for renal transplantation because of the poor prognosis associated with the underlying monoclonal gammopathy [1] and the possibility of recurrent nephropathy after transplantation. A retrospective analysis of a small series of patients with LCDD who had renal

transplantation showed recurrence in five of seven kidney allografts at a median time of 33.3 months after transplantation. The median time to reach end stage renal disease was 10.9 months after the recurrence, suggesting that kidney transplantation should not be an option for LCDD patients [8]. Our patient showed long-term benefit from the grafting despite early recurrence of LHCDD after transplantation. This may be because of varying fibrogenic activities of the deposited immunoglobulin chains [9]. The answer to the questions of whether or not the treatment used for the associated myeloma has any beneficial effect on disease progression, or if the immunosuppressive therapy used against graft rejection has any effect on disease activity or the subsequent development of myeloma or amyloidosis, remain unanswered. In patients with monoclonal gammopathy of undetermined significance, post-transplantation immunosuppression can affect T-cell regulation and, hence, proliferation of the plasma cell clone, which may turn into myeloma [10] and AL-amyloidosis [11].

This case was unusual in that the evidence suggesting the patient's underlying disorder (and likely the cause of his native kidney failure) was present in the biopsy of the transplanted kidney. This fact emphasizes the need to establish before transplantation the diagnosis of the native renal disease, because this has important consequences for proper treatment and prognosis. In addition, the present case serves as a reminder that LHCDD and HCDD should always enter the differential diagnosis of a patient with nodular glomerulosclerosis, hypogammaglobulinaemia and hypocomplementaemia. Careful immunofluorescence studies, using a panel of antisera specific for individual light and heavy chains, should disclose the true diagnosis.

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Conflict of interest statement. None declared.

References

1. Lin J, Markowitz GS, Valeri AM *et al.* Renal monoclonal immunoglobulin deposition disease: the disease spectrum. *J Am Soc Nephrol* 2001; 12: 1482–1492
2. Paueksakon P, Revelo MP, Horn RG, Shappell S, Fogo AB. Monoclonal gammopathy: significance and possible causality in renal disease. *Am J Kidney Dis* 2003; 42: 87–95
3. Tsuzuki K. Role of mizoribine in renal transplantation. *Pediatr Int* 2002; 44: 224–231
4. Buxbaum J, Gallo G. Nonamyloidotic monoclonal immunoglobulin deposition disease. Lightchain, heavy chain, and light and heavy chain deposition diseases. *Hematol Oncol Clin North Am* 1999; 13: 1235–1248
5. Hall CL, Peat DS. Light chain deposit disease: a frequent cause of diagnostic difficulty. *Nephrol Dial Transplant* 2001; 16: 1939–1941

6. JN B. Abnormal immunoglobulin synthesis in monoclonal immunoglobulin light chain and light and heavy chain deposition disease. *Amyloid* 2001; 8: 84–93
7. Soma J, Sato K, Sakuma T *et al.* Immunoglobulin γ 3-heavy chain deposition disease: report of a case and relationship with hypocomplementemia. *Am J Kidney Dis* 2004; 43: 10–16
8. Leung N, Lager DJ, Gertz MA, Wilson K, Kanakiriya S, Fervenza FC. Long-term outcome of renal transplantation in lightchain deposition disease. *Am J Kidney Dis* 2004; 43: 147–153
9. Ronco PM, Alyanakian MA, Mougenot B, Aucouturier P. Light chain deposition disease: a model of glomerulosclerosis defined at the molecular level. *J Am Soc Nephrol* 2001; 12: 1558–1565
10. Rostaing L, Modesto A, Abbal M, Durand D. Long-term follow-up of monoclonal gammopathy of undetermined significance in transplant patients. *Am J Nephrol* 1994; 14: 187–191
11. Dysseleer A, Michaux L, Cosyns JP, Goffin E, Hermans C, Pirson Y. Benign monoclonal gammopathy turning to AL amyloidosis after kidney transplantation. *Am J Kidney Dis* 1999; 34: 166–169

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