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CASE REPORT

Recurrence of light chain deposit disease after renal allograft transplantation: potential role of rituximab?

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Summary

Light chain deposit disease (LCDD) is a monoclonal plasma cell disorder characterized by tissue deposition of nonamyloid immunoglobulin light chains, predominantly kappa chains, causing renal insufficiency. LCDD reoccurs almost invariably after renal grafting, leading to early graft loss, usually within a time span of months to years. We describe a female patient with LCDD who lost her first living donor graft after 1 year due to extensive recurrence of kappa chain deposition. Rituximab was administered on the seventh day after her second transplantation with a graft from a deceased donor, in order to prevent early recurrence of LCDD. The 2-year protocol biopsy – similarly to the completely normal 1-year protocol biopsy – revealed persistent absence of light chain deposition on light microscopy but immunohistochemical staining and electron microscopy showed very mild recurrence of light chain deposits. A second 4-week course of rituximab was repeated because of these electron microscopic findings. Subsequently, free kappa light chain concentration decreased from 693 to 74 mg/l and remained low 4 months after completion of therapy. Rituximab could be considered for delaying early LCDD recurrence in patients in whom treatment of the underlying bone marrow disorder failed or is contraindicated, but maintenance therapy is apparently necessary to consolidate this response.

Case

At the age of 51 a female patient was diagnosed with chronic renal insufficiency grade III because of kappa light chain deposition in her kidneys. No evidence of other organ dysfunction or failure (liver, heart, nervous system, intestine) because of light chain deposit disease (LCDD) was present at the time of diagnosis. Bone marrow examination showed a small monoclonal plasma cell population (4%) without evidence of manifest myeloma invasion. Melphalan-methylprednisolon therapy was commenced but discontinued after three courses because of bone marrow toxicity and subjective intolerance. Subsequently, a combination chemotherapeutic regimen containing vincristine-doxorubicin-dexamethasone (VAD) was attempted but also stopped because of side-effects. No other type of chemotherapy was attempted because of evident lack of extra-renal organ dysfunction. Ten years later, in 1998, a maculopathy developed, characterized by retinal pigment epithelium detachments with mild visual impairment. This ocular pathology was interpreted as associated with LCDD [1]. In August 1998, a pre-emptive transplantation was performed because of end-stage renal failure with a kidney donated by her spouse (four of six HLA mismatches: two A-, one B- and one DR-mm). Informed consent with regard to the risk of disease recurrence was obtained from both donor and recipient. The postoperative course was complicated by one episode of acute rejection (on day 9), promptly responding to treatment with antithymocyte immunoglobulins. Maintenance immunosuppression consisted of tacrolimus, mycophenolate mofetil and corticosteroids. One year later, a renal biopsy was obtained because of graft function deterioration and new onset low-grade proteinuria (0.6 g per

24 h) containing an excess of kappa light chains on immunofixation electrophoresis. Renal histology confirmed recurrence of LCDD in the graft with eosinophilic Congo red-negative depositions around the tubular basement membrane, arterioles and glomeruli (Fig. 1a) and positive immunostaining of kappa light chains (Fig. 1b). Electron microscopy confirmed the changes noted on light microscopy (Fig. 1c). Another year later, chronic peritoneal dialysis therapy was commenced because of graft failure. In April 2004, a second transplantation was performed with a kidney from a deceased male donor (3/6 HLA mismatches: two A-, one B- and zero DR-mm). Initial immunosuppression consisted of anti-CD25 monoclonal antibody induction (basiliximab), tacrolimus, mycophenolate mofetil and corticosteroids. Because of early LCDD recurrence in the first graft, it was hypothesized that the additional use of rituximab as a specific anti-CD20 monoclonal antibody, could potentially further suppress the small monoclonal B-cell/plasma cell population responsible for the production of aberrant kappa light chains and hence prevent or delay disease recurrence in the second graft. The relatively mild side-effect profile of rituximab and the potential additional benefit for prevention of acute rejection, strengthened this decision. Autologous blood stem cell transplantation was not considered an option mainly because of the patient's age and her personal apprehension. Four weekly courses of rituximab (375 mg/m^2 body surface) were administered, starting on day 7 postoperative and were subjectively well tolerated. B cells were completely absent 10 weeks after rituximab therapy [CD19(+) cells = 0] while T lymphocytes had decreased [Total CD3(+) cells: 474 cells/mm^3 (57.5%); CD4(+) cells: 290/mm^3 (35.3%); CD8(+) cells: 152/mm^3 (18.5%)]. The postoperative clinical course was complicated by stress fractures of the sixth and seventh dorsal vertebrae (2 months post-transplantation) and two episodes of acute bacterial pyelonephritis of the failed first graft; the latter was therefore electively removed in February 2005. Graft function remained stable during the following 2 years (mean serum creatinine 1.5 mg/dl, calculated creatinine clearance 32 ml/min); a low-grade proteinuria (0.12 g per 24 h) persisted but without evidence of kappa light chains. The patient was clinically doing well without symptoms of extra-renal organ dysfunction due to LCDD except for the stable maculopathy. Three months after transplantation and again 1 and 2 years after transplantation, routine protocol biopsies were obtained with a stable graft function. Light microscopy of the 1-year biopsy demonstrated mild chronic rejection (Banff 2001 grade I) without any evidence of light chain deposition. Electron microscopy confirmed the absence of electron dense deposits in the glomerular and tubular basement membranes (Fig. 2a–c). Because of

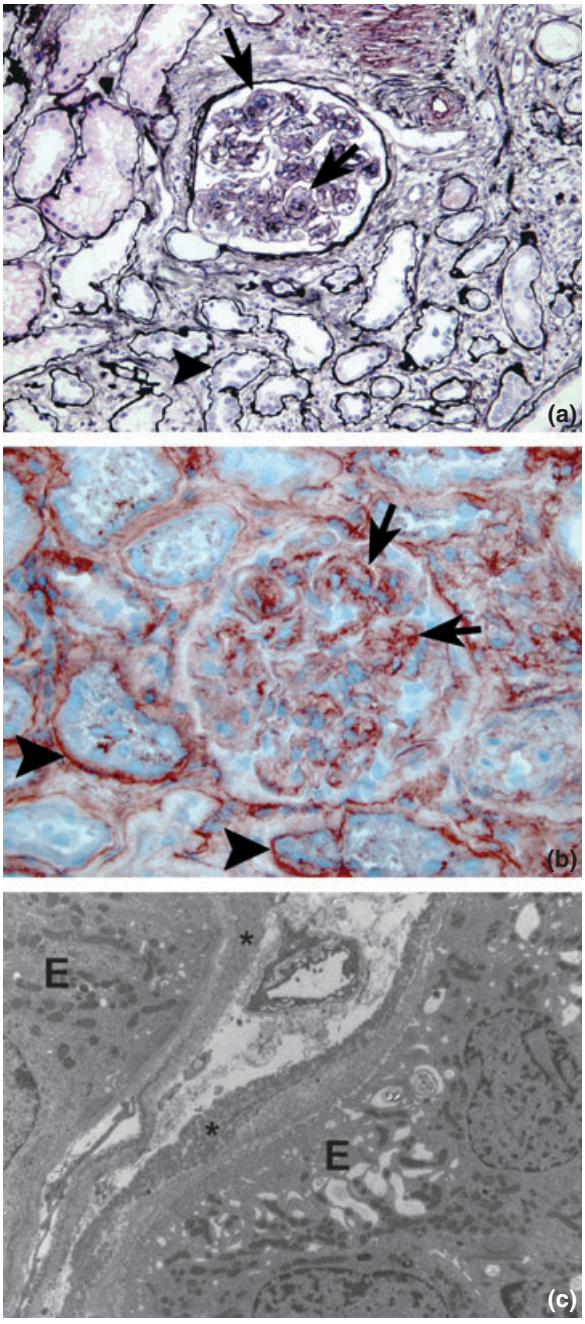

Figure 1 Recurrent kappa deposition in the first renal allograft after 1 year. (a) Silver methenamine stain: hypercellular glomeruli with eosinophilic deposits in the glomerular capillary wall (arrows). Note the slightly thickened tubular basement membranes (arrowheads; original magnification 200×). (b) Immunohistochemistry with monoclonal antibodies against kappa light chains (dilution 1/25, frozen sections; Becton Dickinson Immunocytometry Systems, San Jose, CA, USA): strong, linear anti-kappa positivity along tubular basement membranes (arrowheads) and glomerular basement membrane (arrows; original magnification 400×). (c) Electron microscopy: dense, fine granular deposits in the tubular basement membrane of both tubuli (asterisk; E: tubular epithelium; original magnification 3000×).

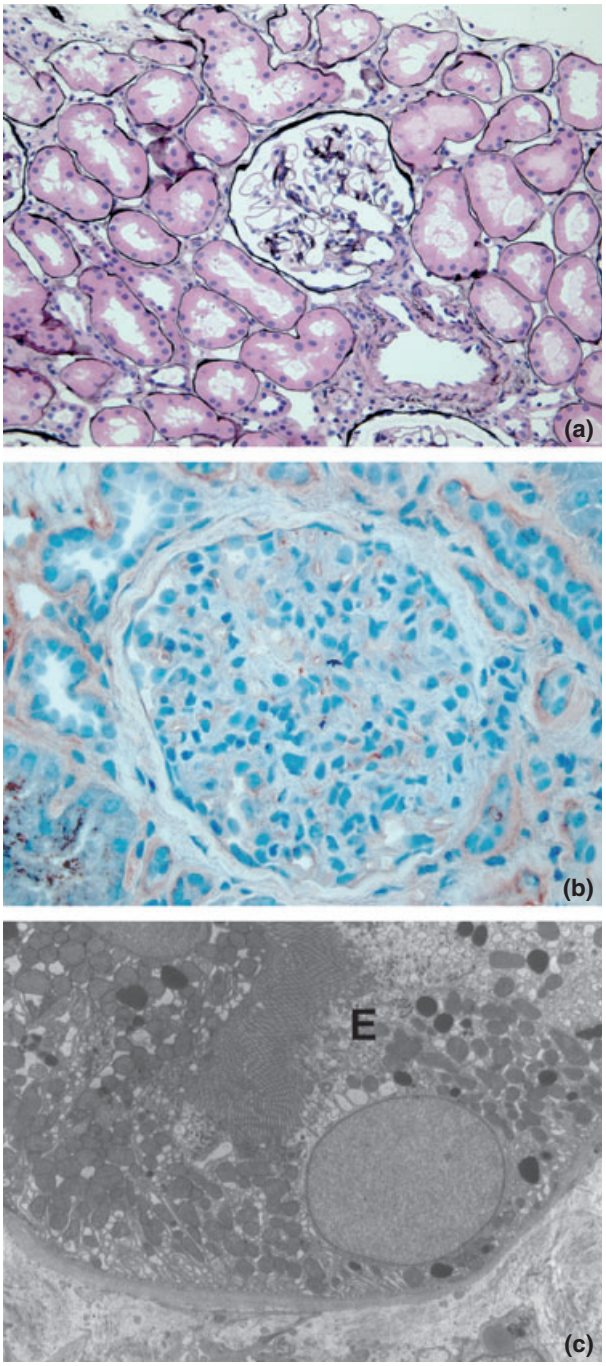

Figure 2 Second renal allograft: the protocol biopsy at 1 year shows no evidence of recurrent light chain deposit disease. (a) Silver methenamine stain (original magnification 200×). (b) Immunohistochemistry with monoclonal antibodies against kappa light chains (original magnification 400×). (c) Electron microscopy (original magnification 3000×; E: tubular epithelium).

these histological findings, the stable graft function and absence of proteinuria and a persistently low B-cell count [(CD19(+) B cells: 11/mm^3 (1.5%); total CD3(+) T cells: 475 cells/mm^3 (65.1%)], it was decided not to repeat rituximab administration at 1 year post-transplantation. After an uneventful second year, light microscopy of the 2-year protocol biopsy (serum creatinine 1.52 mg/dl) still showed signs of mild chronic rejection Banff 2001 grade I, but no signs of light chain deposition (Fig. 3a). Surprisingly, immunohistochemical staining did reveal an excess kappa light chain positivity along the tubular basement membrane and to a lesser extent in the glomeruli (Fig. 3b). Electron microscopy confirmed the presence of small electron dense deposits in the tubular and glomerular basement membrane (Fig. 3c). B-lymphocyte count had meanwhile further increased [CD19(+) cells: 34/mm^3 (4.6%); total CD3(+) cells: 417 cells/mm^3 (55.6%); CD4(+) cells: 226/mm^3 (30.0%); CD8(+) cells: 151/mm^3 (20.1%)]. Immunofixation electrophoresis did not demonstrate kappa light chains in serum nor in urine. However, using a nephelometric assay (Freelite^{TM}; The Binding Site Ltd, Birmingham, UK) for quantifying free light chains, an increased concentration of free kappa light chains was found: 547 mg/l (normal range: 3.3–19.4) with normal free lambda chain concentrations (15.2 mg/l; normal range: 5.7–26.3) and an increased free kappa/lambda ratio of 35.9 (normal range: 0.3–1.2). Repeat bone marrow examination revealed a monoclonal plasma cell population (6.3%), monotypic on kappa light chain staining. Because of these findings, it was decided to repeat 4 weekly doses of rituximab (375 mg/m^2 body surface) therapy 2 years after transplantation in order to try to prevent further progression of delayed LCDD recurrence in the graft. Free kappa light chain concentration dropped from 693 (with a free kappa/lambda ratio of 36) to 106 mg/l (kappa/lambda ratio of 5.6) 1 month after completion of therapy and remained low 4 months later at 74 mg/l (kappa/lambda ratio of 2.27). Two weeks after completion, B lymphocytes had again disappeared from peripheral blood [CD19(+) cells: 0/mm^3 (0%); total CD3(+) cells: 392 cells/mm^3 (47.1%); CD4(+) cells: 232/mm^3 (27.9%); CD8(+) cells: 145/mm^3 (17.4%)]. No side-effects occurred with repeated rituximab therapy.

Discussion

Light chain deposit disease is a rare monoclonal plasma cell disorder characterized by tissue deposition of abnormal nonamyloid immunoglobulin (kappa) light chains causing kidney failure and extra-renal manifestations usually involving heart, liver or peripheral nerves [2–5]. Mortality in LCDD is mainly due to cardiac failure, liver involvement or progression to multiple myeloma with a mean survival of approximately 18–22 months irrespective of the type of therapy which usually consists of steroids, cytotoxic agents and plasma exchange [2–5]. LCDD

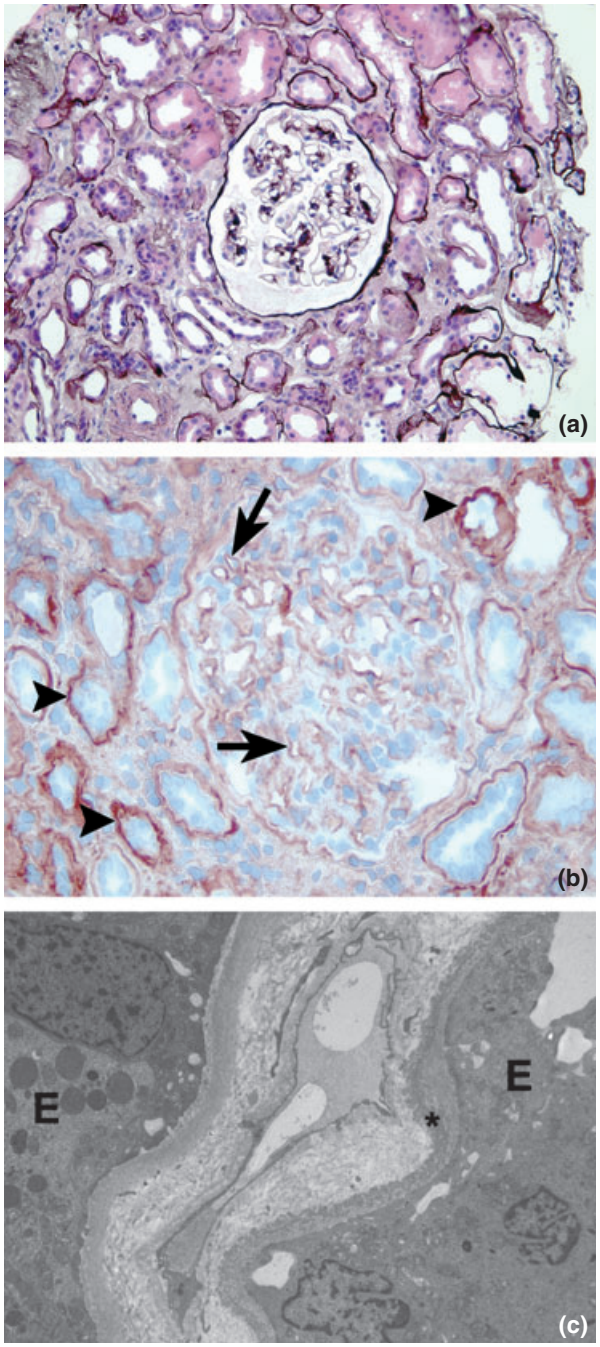

Figure 3 Second renal allograft: the protocol biopsy at 2 years shows mild signs of recurrent light chain deposit disease. (a) Silver methenamine stain: no abnormalities (original magnification 200×). (b) Immunohistochemistry with monoclonal antibodies against kappa light chains: mild to moderate kappa deposition along the glomerular basement membrane (arrows); stronger anti-kappa positivity in the tubular basement membranes (arrowheads; original magnification 400×). (c) Electron microscopy: dense, fine granular deposits in the tubular basement membrane on the right (asterisk); the tubular basement membrane on the left shows no abnormalities (original magnification 3000×; E: tubular epithelium).

almost invariably reoccurs in kidney grafts after a median of 33.3 months (range: 2–45) resulting in severe proteinuria and subsequent graft failure [6]. Therefore, renal transplantation is not routinely advocated in patients with LCDD, except in case of a relatively benign clinical course or in situations where the underlying bone marrow disorder (lymphoproliferative disorders, multiple myeloma) is treated simultaneously [6].

Rituximab is an anti-CD20 monoclonal antibody used successfully in the treatment of non-Hodgkin lymphoma, post-transplantation lymphoproliferative disease (PTLD), ABO-incompatible renal transplantation, different types of primary and secondary glomerulonephritis and autoimmune haemolytic anaemia [7,8]. Although anti-CD20 expression is mainly restricted to pre-B cells and mature B cells, more studies demonstrate expression of CD20 on plasma blasts and stimulated plasma cells and activity of rituximab in plasma cell disorders [9–11].

We demonstrated in a single patient with a relatively benign form of LCDD, as illustrated by the prolonged clinical course, that treatment with rituximab commenced on day 7 after transplantation was capable of at least delaying reappearance of LCDD in her second allograft as opposed to her first graft that had extensive recurrence of light chain deposition within 1 year. Of course, this single case report does not prove a causal relationship between the use of rituximab and the delayed recurrence of light chain disease. Several factors could have influenced the timing of LCDD recurrence in both grafts: living versus deceased donor kidney, acute rejection of the first graft, the use of basiliximab induction for the second graft, donor characteristics and transplantation-related characteristics like HLA matching, warm ischemia time, etc. Despite these limitations, the fact that even after 2 years, no light microscopic depositions were visible in the protocol biopsy and the absence of light chain proteinuria, at least suggest a delaying effect of anti-CD20 antibody therapy. Moreover, the renewed increase in B-cell count after 2 years, concurring with the appearance of electron dense deposits on electron microscopy, suggest a possible link between the two. In retrospect, repeating the rituximab treatment at 1 year post-transplantation could have been a superior strategy, even when taking into account the prolonged half-life of rituximab in case of reduced renal (graft) function [12] and the required time for B-cell recovery [13]. Because patients with LCDD are so seldom transplanted, it is very unlikely that prospective randomized studies examining the efficacy and dosing frequency of rituximab in the prevention of LCDD recurrence will be performed.

We propose that patients with LCDD who failed treatment of the underlying bone marrow disorder and receive a renal allograft, could potentially benefit from induction

therapy with rituximab by delaying recurrent light chain deposition and preventing allograft rejection with an acceptable low risk of serious drug-related side-effects. Nevertheless given the potential risks associated with B-cell depletion and the reported variability regarding time to LCDD recurrence, cautious interpretation of this limited experience is necessary. Given the insidious course of light chain deposition disease, the performance of repeat protocol biopsies as a surveillance instrument is strongly advocated. Electron microscopy is more sensitive than light microscopy for detecting early disease recurrence and could be used for guiding additional treatment with rituximab. Finally, regular monitoring of B-cell numbers after rituximab therapy could be used to detect early reconstitution of B-lymphocyte populations as a potential indicator of renewed risk for increased disease activity. The use of nephelometric assays to quantify free light chains might prove a sensitive follow-up method in patients without overt light chain detected by immunofixation. However, more reports on clinical experience are necessary in order to establish some guidelines how to delay (or prevent) LCDD recurrence in renal allografts by using anti-CD20 monoclonal antibodies.

Conflict of interest

None of the authors has declared a conflict of interest in relation to the manuscript.

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