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CASE REPORT

Monoclonal gammopathy of renal significance with light-chain deposition disease diagnosed postrenal transplant: a diagnostic and therapeutic challenge

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Summary

Patients with light-chain deposition disease (LCDD) frequently do not meet criteria for myeloma. In such cases, despite low tumor burden, the circulating monoclonal immunoglobulins cause renal damage, are responsible for post-transplant recurrence, and are rightly categorized as monoclonal gammopathy of renal significance (MGRS) requiring chemotherapy. A 65-year male with uncharacterized nodular glomerulopathy presented with proteinuria 3 years postrenal transplant. His allograft biopsies were diagnostic of light-chain deposition disease (likely recurrent), and in the absence of myeloma, he was labeled as MGRS. Based on the limited literature available, he was treated with bortezomib which resulted in normalization of serum-free light-chain ratios and resolution of proteinuria. He, however, later succumbed to complications of chemotherapy. This case highlights the diagnostic difficulties in LCDD, the importance of an accurate pretransplant diagnosis, and treatment of the malignant clone, in the absence of which post-transplant management of recurrence is challenging with poor outcomes.

Background

Monoclonal gammopathy of renal significance (MGRS) is a recently introduced clinical term aimed to identify patients with a small B-cell clone that does not meet criteria for myeloma or lymphoma, however, causes significant renal disease due to deposition of monoclonal immunoglobulins (MIg) [1,2]. MGRS is associated with a wide spectrum of glomerulopathies, classified by the type, localization, and organization of the deposited MIg [3]. Most of these, with the exception of AL amyloidosis, are associated with low cancer-related mortality, and treatment is indicated mainly for the preservation of native kidney function and prevention of recurrence in the transplanted graft. Clinical trials are rare, and treatment guidelines are based on individual experiences. We present our experience with a case of light-chain deposition disease (LCDD) with MGRS diagnosed in the post-transplant period and discuss the diagnostic and therapeutic challenges in this clinical scenario.

Case report

A 65-year old male underwent a live-related renal allograft transplantation at our institution in 2009. He had a history of proteinuric illness since 2004 with biopsy-proven nodular glomerulosclerosis without further characterization reported at another institution. By 2008, he had progressed to stage five chronic kidney disease and was on renal replacement therapy. In view of the histology, he was investigated for diabetes mellitus and multiple myeloma (serum/urine protein electrophoresis and skeletal survey) which were all negative.

The post-transplant period was initially uneventful with a baseline serum creatinine of 0.7 mg/dL on triple

drug immunosuppression [tacrolimus, mycophenolate mofetil (MMF), and prednisolone]. In 2012, he developed pedal edema and was first detected to have proteinuria with a 24-h urinary protein of 830 mg which rapidly progressed to 2.4 gm in a span of three months with a serum creatinine of 1.3 mg/dl. An allograft biopsy was performed for the indication of graft proteinuria and mild graft dysfunction. The glomeruli displayed minimal mesangial expansion with minimal mesangial staining for kappa on immunofluorescence. There was focal acute tubular injury and minimal interstitial fibrosis and tubular atrophy. There was no evidence of rejection, and C4d was negative. No tissue was available for electron microscopy (Fig. 1a and b). The pedal edema persisted, and a repeat biopsy was performed two months later. At this point, he was normotensive and his investigations were as follows: serum creatinine 1.4 mg %; 24-h urine protein 1.2 g/24 h; urine examination 3+ proteinuria; 5-6 RBCs per high power field. Serum C3 was normal (98 mg %). On histology, all the glomeruli now showed mild to moderate mesangial expansion with occasional mesangial nodule formation and irregular capillary wall thickening. The nodules were positive on periodic schiff's (PAS) stain, variably argyrophilic with peripheral lamellations, and were not congophilic. There were no features suggestive of rejection, and C4d staining was negative in the peritubular capillaries. There was focal tubular atrophy with mild thickening of tubular basement membranes. Immunofluorescence staining showed 3+ (scale of 0–3+) kappa uptake in glomerular capillary walls and mesangium along with tubular basement membrane and arterial wall staining, while lambda was negative. There was no deposition of any other antisera (IgG, IgM, IgA, C3, and C1q) studied. Electron microscopy showed characteristic dark, granular deposits in a subendothelial location, confirming the pathological diagnosis of light-chain deposition disease (LCDD) (Fig. 1c–f).

Investigations for a plasma cell dyscrasia were again initiated based on the histology. There was no detectable monoclonal paraprotein on serum or urine electrophoresis. Bone marrow examination showed 5% plasma cells. Skeletal survey did not reveal any lytic bony lesions. However, serum-free light-chain (FLC) assay showed elevated serum FLC with a kappa to lambda ratio of 4.8 (Normal: 0.26–1.65) consistent with the light-chain deposition pattern noted on biopsy.

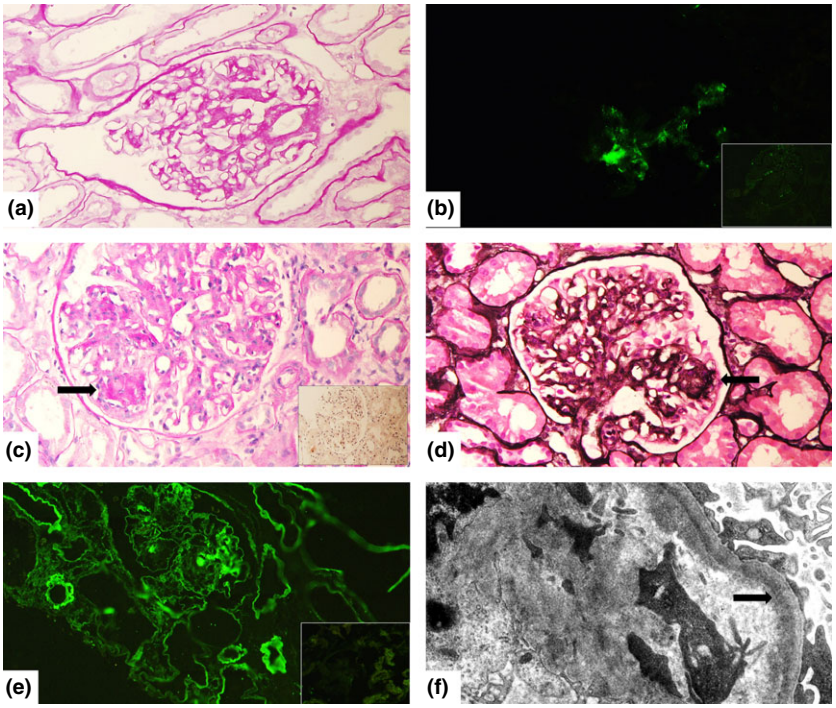

Figure 1 (a) The initial biopsy showed only mild mesangial expansion. PAS, ×200 (b) Mild mesangial staining for Kappa was noted on immunofluorescence. Staining for lambda was negative (inset) (c) The second kidney biopsy shows mesangial hypercellularity with nodule formation. PAS, ×200. The nodules were negative for Congo red (inset, ×200). (d) The nodules showed positivity with silver methenamine. (e) Immunofluorescence for kappa was positive along tubular basement membranes and glomerular capillary walls. Other antisera including lambda were negative (inset) (f) Ultrastructure photomicrograph showing granular electron dense deposits along the subendothelial aspect of the glomerular basement membrane with secondary podocyte effacement.

Table 1. Treatment and outcomes of patients with recurrent MIDD post-transplant.

	Duration to recurrence post-transplant	Myeloma workup	Chemotherapy	Outcome (time post-transplant)
Patient 1 [9]	26 months	M band positive, 15% plasma cells	None	Deteriorated, started on maintenance hemodialysis (?)
Patient 2 [6]	33 months	M band positive; 7 % plasma cells	None	Died (37 months)
Patient 3 [6]	45 months	M band positive, 10–15% plasma cells	None; Hemodialysis	Died of myelodysplastic syndrome (92 months)
Patient 4 [6]	34 months	No M band; 3–5% plasma cells	None; Hemodialysis	Died (72 months)
Patient 5 [6]	3 months	No M band; 5% plasma cells	None; Allograft nephrectomy; Peritoneal dialysis	Developed amyloidosis (60 months)
Patient 6 [7]	2 months	MGUS	None; Allograft nephrectomy; Peritoneal dialysis	Progressed to myeloma; Died (36 months)
Patient 7 [10]	43 months	Not available	Dexamethasone and melphalan for 9 months, followed by lenalidomide for 3 months and bortezomib for 5 months	Significant reduction in serum-free kappa; Allograft function slightly decreased; Serum creatinine 1.5 mg/dl (73 months)
Patient 8 [10]	11 months	Not available	Prednisone for concurrent rejection	Died (37 months); Serum creatinine 2.3 mg/dl
Patient 9 [10]	7 months	Direct myeloma infiltration of allograft	Bortezomib and dexamethasone	Ineffective, lost allograft, and died of refractory multiple myeloma (8 months)
Current case	36 months	MGRS	Bortezomib	Normalization of serum-free light-chain ratios, histological regression of light-chain deposits, and reduction in proteinuria Died of ATT-induced liver failure (12 months)

Retrospectively, it was now clear that the normal glomerular morphology with mesangial kappa deposition seen in the first post-transplant biopsy represented early disease with progression to the more classical nodular glomerulosclerosis of LCDD. Not having met criteria for multiple myeloma, our patient was classified as a case of Monoclonal gammopathy of renal significance manifesting as post-transplant LCDD, possibly recurrent.

He was treated with five cycles of Bortezomib with resolution of edema and proteinuria and normalization of serum FLC ratio. Toward the end of the course, he developed leucopenia and rashes, followed by cytomegalovirus retinitis for which MMF was initially withdrawn, I.V. Ganciclovir was started, and later, MMF was reintroduced at a lower dose. Two months later, he developed sputum acid fast bacillus positive pulmonary tuberculosis for which modified antitubercular treatment was started. A repeat biopsy for an acute rise in creatinine demonstrated an eosinophil rich acute interstitial nephritis (likely drug induced) with persistence of the nodular glomerulosclerosis; however, immunofluorescence for kappa light chains was now negative. He later developed drug-induced acute liver failure and expired following a fatal bout of massive hemoptysis in March 2013.

Discussion

Renal diseases with deposition or precipitation of monoclonal immunoglobulins (Ig) are classified histologically based on the nature of the deposits as *organized* (crystals: cast nephropathy, light-chain proximal tubulopathy, crystal storing histiocytosis; fibrillar: light-chain amyloidosis, fibrillary glomerulonephritis; microtubular: type I and II cryoglobulinemia, immunotactoid glomerulonephritis) and *nonorganized or granular* [monoclonal immunoglobulin deposition disease (MIDD), proliferative glomerulonephritis with monoclonal Ig deposits, and Waldenstroms macroglobulinemia].

In MIDD, morphological manifestations such as mesangio-proliferative, membrano-proliferative, and even minimal change patterns may precede the classical pattern of nodular mesangial sclerosis as was seen in our case and can contribute to misdiagnosis [4]. Full immunofluorescence panel including kappa and lambda light chains is required to demonstrate the monoclonal protein deposition, and any amount of monotypic light-chain deposition should prompt a search for a source (plasma cell dyscrasia/lymphoma) in case of unexplained proteinuria. In 35 % cases of MIDD, basic myeloma workup (urine and serum

electrophoresis, skeletal survey, and bone marrow plasma cells) may be negative and an abnormal serum-free light-chain assay may be the only indication of the presence of a monoclonal paraprotein.

The term 'MGRS – monoclonal gammopathy of renal significance' was recently coined to describe cases of monoclonal paraprotein-related kidney disease which do not fulfill criteria for multiple myeloma [1]. These cases were initially diagnosed as 'MGUS – monoclonal gammopathy of undetermined significance' based on hematological criteria and did not receive treatment due to low tumor burden. The toxic monoclonal protein, however, produced by the 'dangerous small B-cell clone' results in significant renal morbidity, as demonstrated by Heilman *et al.* [5] in their study on long-term follow-up of nineteen patients with light-chain deposition disease, 63% of whom were associated with 'MGUS'. Although the overall patient survival was good with 70% 5-year survival rate, the renal survival was only 67% at 1 year and 37% at 5 years. This high rate of progression to end-stage renal disease was attributed to absent or inadequate chemotherapy in these cases.

Clinical experiences from the few patients with LCDD who have undergone transplantation show that failure to control light-chain production results in rapid recurrence of disease in the allograft [6–9]. Leung *et al.* [6] reviewed seven patients of LCDD who underwent renal transplantation. One patient had an associated multiple myeloma and received melphalan pretransplant, while the remaining six were hematologically classified as MGUS and did not receive any chemotherapy. Five of the seven patients developed a recurrence with a median time to recurrence of 33.3 months (2.9–45.9 months) including four patients with MGUS. They were either maintained on hemodialysis or underwent an allograft nephrectomy, and three of them died later mostly due to sepsis. It is to be noted that none received post-transplant chemotherapy [Table 1]. The authors concluded that renal transplantation should be avoided in patients with LCDD unless measures are taken pretransplant to reduce light-chain production and that chemotherapy post-transplantation is difficult to implement due to complications of increasing immunosuppression. Nasr *et al.* [10] in their review of sixty-four patients with MIDD included three patients of LCDD who had recurred postrenal transplantation and were treated with variable outcomes as described in Table 1.

The latest therapeutic proposals for MGRS recommend treatment decisions to be based on the degree of renal impairment [11]. Three to four cycles of bortezomib-based regimens followed by high-dose melphalan (HDM)/autologous stem cell transplantation (ASCT) are recommended prior to the transplant. Achieving the best hematological response with complete sustained remission appears to be the deciding factor for long-term allograft function [12].

In our case, bortezomib successfully treated the malignant clone with complete hematological response, normalization of serum-free light-chain ratio, histological regression of light-chain deposits, and reduction in proteinuria; however, the additional therapy led to a host of infections which were difficult to control, required adjustments of the immunosuppression, and led to the loss of the patient.

This case highlights the importance of diagnosing MGRS and related kidney diseases in the pretransplant period so that the paraprotein secreting clone can be optimally treated. A proper histological workup of all transplant biopsies including light, immunofluorescence, and electron microscopy is essential. Post-transplant management of recurrent MIDD is challenging, and current clinical experience suggests a poor outcome for the graft and/or patient.

Authorship

AN: wrote the paper. DB: contributed to paper and was directly responsible for patient treatment. GS: diagnosed and researched the case and guided paper writing. SKA: responsible for overviewing patient treatment. AKD: overviewed diagnosis and research of the case.

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