LETTER TO THE EDITORS

Monoclonal gammopathy of renal significance with heavy-chain deposition disease in renal allograft: challenges in the diagnosis and management

Lavleen Singh[1], Arun Kumar Subbiah[2], Geetika Singh[1], Soumita Bagchi[2], Amit Kumar Dinda[1] & Sanjay Kumar Agarwal[2]

[1]Department of Pathology, All India Institute of Medical Sciences, New Delhi, India
[2]Department of Nephrology, All India Institute of Medical Sciences, New Delhi, India
E-mail: amit_dinda@yahoo.com

Dear Editors,

Monoclonal gammopathy of renal significance (MGRS) is a paraprotein-associated renal disorder with an underlying onco-hematological condition due to a small B-cell clone. Heavy-chain deposition disease (HCDD) is a rare face of MGRS, especially in the renal transplant setting with little data on management outcomes [1,2]. We herewith present a case of a 42-year-old male patient referred to our institution with subnephrotic proteinuria progressing to end-stage renal disease. A kidney biopsy done elsewhere showed nodular glomerulosclerosis, which was not characterized further. The hematooncological workup suggested the diagnosis of monoclonal gammopathy of undetermined significance (MGUS) in the year 2012. On account of features of chronic kidney disease and normal bone marrow aspiration findings, primary treatment was deferred at that time. He progressed to ESRD in 2013 for which he underwent a live-related renal transplantation in November 2013.

Graft biopsy, 22 months post-transplantation (August 2015) for the indication of subnephrotic range proteinuria revealed nodular glomerulosclerosis (Fig. 1a, periodic acid schiff stain ×40) with negative staining for silver methenamine (Fig. 1b, silver methenamine). The immunofluorescence (IF) studies showed deposition of IgG (Fig. 1c) in the absence of other heavy and, light chains which suggested the diagnosis of HCDD. The diagnosis was further confirmed on ultrastructural evaluation, showing, powdery electron-dense deposits in the glomerular basement membrane and on the outer aspect of the tubular basement membrane (Fig. 1d). Serum protein electrophoresis (SPEP) at this point was positive for M band and free light chain assay revealed significant kappa predominance (Kappa >3990; Lambda= 56 mg/l).

Patient was managed with bortezomib injections 1.3 mg/m^2 weekly along with oral thalidomide 50 mg daily (for 4 months) and dexamethasone 40 mg weekly. Patient is still being continued on bortezomib and dexamethasone maintenance. The patient had stable serum creatinine 1.6 mg% with a significant reduction in proteinuria (480 mg) 6 months and 1 year later. The serum creatinine continues to be stable at 1.6 mg% and the last documented proteinuria was 540 mg/day in April 2018. The patient is in hematological remission and last documented SPEP was negative in October 2018 and free light chain ratio was normal.

The term MGRS was devised to address the management dilemmas associated with the hematological condition, MGUS [1,2]. Monoclonal immunoglobulin deposition diseases (MIDDs) are paraprotein-related disorders characterized by noncongophilic, nonfibrillar electron-dense deposits distributed in various tissues [3]. It includes three entities: LCDD, LHCDD, and HCDD [4]. The deposits in HCDD comprise of a truncated heavy chain (HC) with CH1 deletion and unusual amino acid substitutions in the VH region with no associated light chains [5–7].

The IF is diagnostic in MIDDs and characteristically shows monoclonal immunoglobulins (MIg) in the glomerular, tubular, and arterial basement membrane. The ultrastructural examination shows a characteristic powdery electron-dense deposit corresponding to the MIg deposition. The main therapeutic target in MGRS is to suppress the culprit B-cell clone by chemotherapy. Bortezomib-based chemotherapy, which does not require dose adaptation to the eGFR, should be the first-line treatment in MGRS. MGRS is no longer

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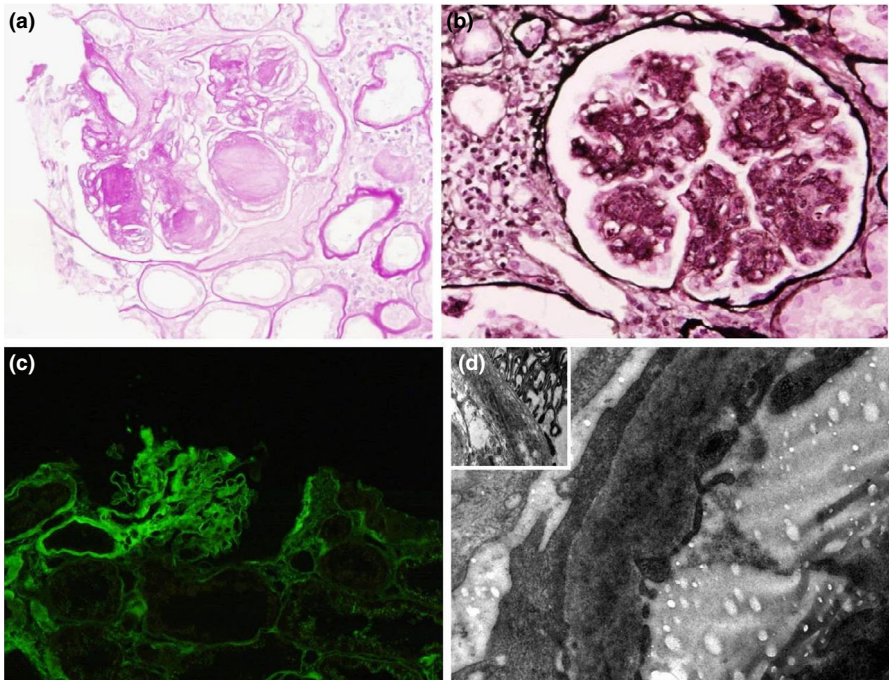

Figure 1 A case of heavy-chain deposition disease presenting as monoclonal gammopathy of renal significance. A representative glomerulus with nodular sclerosing glomerulosclerosis (a, periodic acid schiff ×40). The nodules are negative on silver methenamine (b, silver methenamine ×40). There is linear deposition of IgG (3+, 0–3 scale) on immunofluorescence (c, FITC-IgG staining, ×20). Ultrastructural examination shows powdery dense deposits in the glomerular basement membrane (d, transmission electron microscope, uranyl acetate lead citrate ×5000) and tubular basement membrane (d inset, transmission electron microscope, uranyl acetate lead citrate ×5000).

considered contraindication for renal transplantation in patients with the good hematological response as the risk of patient succumbing to malignant clone is low.

Poor renal outcomes were noted in HCDD before the widespread usage of bortezomib-based chemotherapy as evidenced by various cases published until 2011 [3,8]. Patel *et al.* [9] advocated the use of bortezomib-based chemotherapy for the treatment of HCDD based on their experience of three cases with the longest follow-up of 2.5 years. The index case showed a significant reduction in proteinuria and stable graft function 5 years post-transplantation with bortezomib-based chemotherapy.

To conclude, detailed IF and ultrastructural studies are a must for accurate characterization of MGRS. Bortezomib-based chemotherapy may induce long-term hematological and nephrological remission in the renal transplant setting.

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