Reviewer's report

Title: Resolution of cast nephropathy following free light chain removal by haemodialysis in a patient with multiple myeloma: a case report.

Version: 3 Date: 1 June 2008

Reviewer: vecihi batuman

I am familiar with the literature and believe that this case meets one of the 9 criteria for evaluation in the journal: Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Has the case been reported coherently?: Yes

Is the case report authentic?: Yes

Is this case worth reporting?: Yes

Is the case report persuasive?: Yes

Does the case report have explanatory value?: No

Does the case report have diagnostic value?: No

Will the case report make a difference to clinical practice?: Yes

Is the anonymity of the patient protected?: Yes

Comments to authors:

This is an interesting case report with potentially significant clinical implications for treatment of acute cast nephropathy in patients with multiple myeloma. The authors treated their patient with hydration, chemotherapy including dexamethasone and thalidomide, and free light chain removal using high cut-off hemodialysis. The high cut-off hemodialysis, a technique introduced by the authors, once again proved effective in removing light chains and reducing the light chain burden significantly. It is noteworthy that after initiation of chemotherapy even before dialysis, serum kappa FLC concentration of 15,700 mg/L was reduced to 1,990mg/L 5 days after initiation of the first pulse. Dialysis was then initiated, and after 16 treatments and 33 days after the start of chemotherapy, serum kappa FLC concentrations were further reduced to less than 5% of the starting level (500mg/L) and maintained below this level.

Renal biopsy demonstrated cast nephropathy and significant interstitial inflammatory cell infiltrate with diffuse fibrosis and tubular atrophy. A repeat kidney biopsy 6 weeks later showed complete resolution of the intratubular casts,
and partial resolution of the interstitial inflammatory infiltrate. However, the
degree of interstitial fibrosis and tubular atrophy remained unchanged. Dialysis
was discontinued after a total of 22 treatments with high cut-off dialyzer and
standard high flux dialysis for an additional 5 days. The patient’s serum
creatinine was 872 µmol/L and serum urea 31.5 mmol/L on presentation. One
year after discontinuation of dialysis the patient’s eGFR was 8 ml/min/1.73 m²
based on a serum creatinine of 540 µmol/L, with only a modest improvement and
the patient still in end-stage kidney disease (stage V according to NKF/KDOQI
classification).

CRITIQUE
This may well be only the second reported case in the medical literature
demonstrating by biopsy resolution of renal tubular casts in acute cast
nephropathy associated with multiple myeloma. The first case reported by Rose
et al in 1987 (cited by the authors in reference 6) again demonstrated resolution
of the casts in a repeat kidney biopsy in a 54 year old woman 8 months after the
initial presentation with severe acute oliguric renal failure (creatinine 2020
µmol/L). Similarly, light chain burden was markedly reduced with the aid of
chemotherapy (VAD) as well as peritoneal dialysis, another strategy to remove
serum FLCs more efficiently than conventional hemodialysis.

Different from the current case described by Basnayake et al, the patient
reported by Rose et al had no evidence of interstitial fibrosis and tubule atrophy,
particularly in the follow-up biopsy. Perhaps in more dramatic contrast, and in
agreement with the repeat biopsy findings, this patient had a marked
improvement in her kidney function. At 12 months her serum creatinine was 258
µmol/L (down from the initial value of 2020 µmol/L).

The current report, thus, shows that despite resolution of the casts and
maintenance of low FLC burden the patient remained in end-stage kidney
disease (eGFR 8 ml/min/1.73 m²), consistent with the persistence of interstitial
fibrosis and tubule atrophy. The modest improvement in kidney function
observed relative to presentation was probably through treatment of
superimposed prerenal azotemia by volume repletion, and resolution of acute
inflammatory changes possibly through use of dexamethasone as well as
reduction in her FLC burden on the kidney. Although the patient was taken off
dialysis apparently in deference to her personal preference, most nephrologists
in the US would have continued her on dialysis with eGFR ~ 8 ml/min, a value
well within stage V chronic kidney disease range according to the NKF/KDOQI
staging of CKD.

There are a number of implications of these observations. The first obvious
conclusion is that with the combination of chemotherapy and dialysis, especially
with high-cut off dialyzer, the FLC burden can be reduced dramatically. Second,
reducing FLC burden can result in dramatic resolution of casts (presumably
containing FLCs bound to Tamm-Horsfall proteins). Disappearance of casts,
however, may or may not result in reversal of kidney failure. In the 1987 case by
Rose et al there was marked improvement in kidney function, but upon
presentation their patient was also on indomethacin, which may have contributed to the severity of her acute renal failure. Perhaps, a fair conclusion might be that yes, casts may resolve, but cast formation may not be the sole or even the overriding determinant of kidney failure. Interstitial inflammatory cell infiltration, and the subsequent fibrosis and atrophy, most likely mediated by inflammatory cytokines as well as epithelial mesenchymal transformation as a consequence of excessive endocytosis of light chains in proximal tubule epithelia may be more important (as reported in a number of studies from this reviewer’s laboratory).

This case along with the earlier report from Rose et al contributes to our understanding of kidney involvement in myeloma and the role of FLC burden in the formation of renal casts. The paper would be more compelling if the authors were to contrast their observations with the earlier report by Rose et al, and expand their discussion within the context of recent insight into pathophysiologic mechanisms in kidney injury associated with multiple myeloma. In their revision the authors should point out the persistence of severe kidney disease in their patient despite resolution of the casts, and discuss the implications of this observation.

**Quality of written English:** Acceptable

**Declaration of competing interests:**

I declare that I have no competing interests.