CASE REPORT

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Myeloma-induced renal failure: can plasmapheresis help?

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ABSTRACT

Multiple myeloma, a malignant plasma cell disorder, is frequently complicated by renal failure, which has therapeutic and prognostic implications. The most common cause of severe acute renal failure in these patients is myeloma kidney. Pathophysiologically it involves the precipitation of excessive amounts of filtered light chains, leading to tubular injury and intratubular cast formation. We believe that plasmapheresis, by promptly reducing the serum levels of light chain protein, can prevent further kidney injury, until chemotherapy can fully act.

We present the case of a 53-year-old female patient with myeloma kidney who was admitted with acute kidney injury which improved after plasmapheresis. We also present a brief literature review on this subject.

Key-Words:
Acute kidney injury; multiple myeloma; myeloma kidney; plasmapheresis.

INTRODUCTION

Multiple myeloma is a haematopoietic malignancy characterised by uncontrolled proliferation of terminally differentiated plasma cells in the bone marrow, producing a monoclonal immunoglobulin[1]. Worldwide incidence rates vary from 0.4 to 5 per 100,000 person-years, with rates higher in western than in Asian countries[2]. In the United States, multiple myeloma accounts for approximately one percent of all cancers and about fifteen percent of haematologic malignancies[3]. Renal failure is a common problem in myeloma patients and results in higher mortality. Nearly half of the patients have renal involvement at presentation and much of the damage is irreversible, leading to various degrees of chronic kidney disease[4].

Acute kidney injury in this setting is typically multifactorial, although the most frequent pathology finding is myeloma kidney or cast nephropathy[5]. In this complication, the pathophysiological mechanism involves the intraluminal precipitation of excessive amounts of filtered toxic light chains, leading to tubular injury and intratubular cast formation. The protein casts are formed by filtered light chains and Tamm-Horsfall protein secreted in distal renal tubules[6]. There are other notable contributing factors to renal impairment in this population, with hypercalcaemia, dehydration, sepsis and nephrotoxic drugs common precipitants[7].

Renal failure can also be the result of primary amyloidosis or monoclonal immunoglobulin deposition disease, either light chain deposition disease (LCDD), or more rarely, heavy chain deposition disease[8].

Ultimately, diagnosis of the accurate kidney lesion can only be established by renal biopsy. Although unnecessary for multiple myeloma diagnosis, it provides prognostic considerations in patients with renal involvement, especially as myeloma kidney is associated with a more rapid decline in renal function and shorter survival than other entities[5].

The first general approach to myeloma cast nephropathy has three main aims: to maintain hydration and euvolemia with intravenous fluids to prevent volume depletion and keep a high urine output, avoid toxins and aggressively treat all potential morbid factors, such as infections and hypercalcaemia[8]. These measures are intended to decrease the light chain concentration within the tubular lumen and produce a high urine flow rate to minimise light chain precipitation[7].

The mainstay of treatment is chemotherapy, and in recent years treatment guidelines have shifted towards schemes including the novel agents bortezomib, thalidomide and lenalidomide. Although it seems that immediate removal of large quantities of light chains through extracorporeal clearance could add benefit, evidence showing the effectiveness of plasmapheresis is still conflicting. Nevertheless, there are a few studies and case reports that advocate its use[9].

CASE REPORT

A 53-year-old Caucasian female with a five-year history of unspecified generalised bone pain was referred to the nephrology department for evaluation of a recent elevation in serum creatinine and urea (3.9 mg/dL and 167 mg/dL, respectively). Concomitantly she had a normocytic normochromic anaemia (haemoglobin 9.2 g/dL) and thrombocytopaenia (93,000/µl). Three months before, she had started complaining of malaise, appetite loss and was diagnosed with hypertension, treated with diltiazem 60 mg bid and furosemide 40 mg id. At that time she had only slight anaemia and thrombocytopaenia (Hb 11 g/dl and platelets 111,000 /µl). Other blood and urine tests were normal.

The rapidly progressive renal failure led to her being admitted for diagnostic work-up. On admission she already had a reduced kidney function (creatinine 5.0 mg/dL and urea 255 mg/dL), and prednisone was prescribed as an empirical measure (1 mg/kg/day) for suspected vasculitis, until further diagnostic work-up was completed (± 5 days).

She underwent a renal ultrasound, which showed normal kidney size and morphology. Immune assays were normal or negative to anti-nuclear antibodies (ANA), anti-double stranded DNA antibodies (Anti dsDNA), anti-neutrophil cytoplasmic antibodies (ANCA),

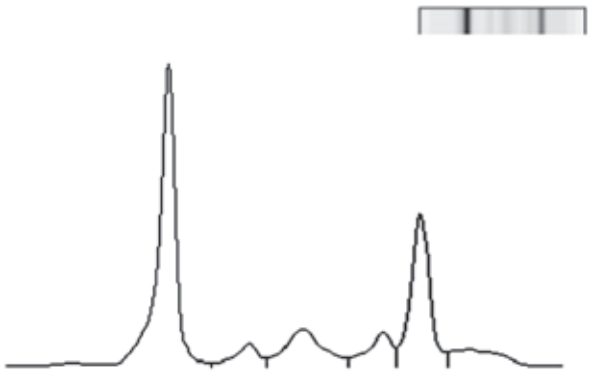

Figure 1

Protein electrophoresis with a narrow peak in the β region.

Antistreptolysin O titre (ASOT), anti-hepatitis C virus (HCV), anti-hepatitis B virus (HBV) and Human Immunodeficiency virus (HIV) 1 and 2. Serum protein electrophoresis revealed a narrow peak with beta migration (Fig. 1) and serum immunofixation confirmed a monoclonal gammopathy immunoglobulin A kappa. Serum free light kappa chains were 578 mg/dl (normal range up to 20 mg/dL). Total calcium was always normal (8.6-9.7 mg/dL), uric acid level was 8.6 mg/dL and her 24-hour proteinuria was 3200 mg. The renal biopsy corroborated the diagnosis of myeloma kidney (Fig. 2 and 3). Bone marrow examination showed 1.5% of dysplastic and aberrant plasma cells.

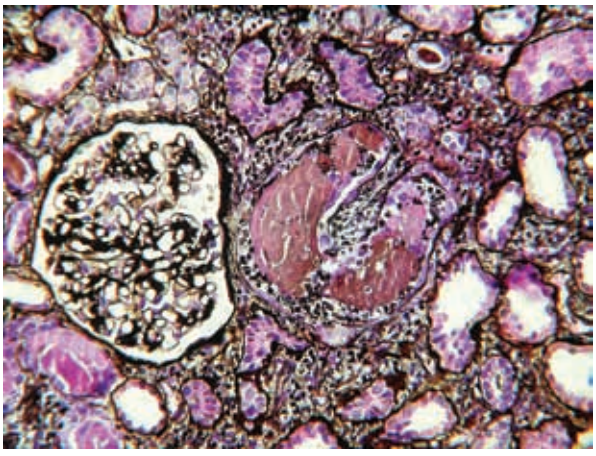

Figure 2

Bowman's capsule thickening, fragmented hyaline casts with some syncytium (Silver ×200).

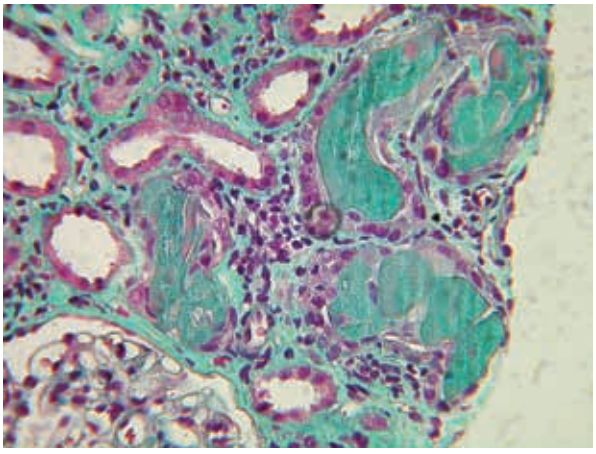

Figure 3

Interstitial fibrosis with mild lymphocyte infiltrate, polychromatic and fragmented casts (Trichrome ×400).

She was intensively hydrated with a goal of over 3L/day urinary output and underwent six plasmapheresis sessions (days 1,2,3,4,6 and 8), exchanging one volume of plasma for 4% albumin each time. Her kidney function improved to a minimum creatinine of 3.3 mg/dL and her serum kappa light chains fell towards normal (lowest level 39 mg/dL). She was found fit to be a bone marrow transplantation candidate, and started chemotherapy with dexamethasone and thalidomide as pretransplant therapeutic scheme. During hospital stay diabetes mellitus secondary to corticotherapy was also diagnosed in a patient probably with previous peripheral insulin resistance.

At hospital discharge she had the following blood test results: haemoglobin 9.6 g/dL, platelets 232,000 /µl, creatinine 3.3 mg/dL, urea 188 mg/dL, total proteins 6.1 g/dL and albumin 4.0 g/dL. She is currently under bortezomib and dexamethasone due to deep vein thrombosis secondary to thalydomide. Her renal function improved, creatinine is now 2.1 mg/dL, and she is awaiting autologous bone marrow transplant.

DISCUSSION

In this patient, from the beginning the challenge was to understand the aetiology of the rapidly progressive acute kidney injury. For a diagnosis of symptomatic multiple myeloma, three criteria must be met: presence of an M-protein in serum and/or urine; presence of 10% or more clonal bone marrow plasma cells; and presence of related organ tissue impairment (increased plasma calcium level, renal insufficiency, anaemia and lytic bone lesions). Approximately 4% of patients may have fewer than 10% bone marrow plasma cells since marrow involvement may be focal, rather than diffuse. A diagnosis of multiple myeloma can be made if other diagnostic criteria are fulfilled, after histopathological confirmation of a soft tissue or bone plasmacytoma[10]. In our patient the bone biopsy showed only 1.5% of plasma cells in the marrow. The diagnosis was possible due to the M component in serum protein electrophoresis with immunofixation confirming a monoclonal gammopathy IgA kappa, renal failure, anaemia and renal histomorphology proving a cast nephropathy pattern.

Filtered free light chain is normally reabsorbed in the proximal tubular cells (PTC) by receptor-mediated endocytosis. Cast nephropathy develops in myeloma as the excess of filtered light chains are both directly cytotoxic to the PTC and indirectly induce an inhibitory effect on endocytosis and release of proinflammatory cytokines, therefore promoting interstitial injury and fibrosis. Injury to the PTC allows escape or overflow of the light chains to the distal nephron, where they interact with Tamm-Horsfall protein and form casts, which can occlude the tubular lumen and promote further local inflammation. Tubular solute composition and tubular flow rates modulate the risk for cast formation, as does urinary acidification, furosemide and urinary sodium and calcium concentration[11].

Multiple myeloma patient's survival decreases in proportion to the severity and chronicity of kidney disease[7]. In cast nephropathy, the pitfall of treatment is to decrease light chain production in order to reduce its likelihood of causing renal damage. In this setting, chemotherapy is the mainstay of treatment. However, its effects take time, and irreversible renal failure might occur meanwhile. Moreover, kidney damage limits further clearance of light chains and a vicious cycle of renal impairment and inability to clear light chains aggravates kidney disease[8]. This is the pathophysiological explanation that suggests extracorporeal removal of large quantities of light chains might break this morbid spiral, and it is the reason why we performed plasmapheresis in this case.

Plasmapheresis has been in use for treating acute myeloma kidney since 1976[12]. Evidence of its effectiveness in patients with acute renal failure due to myeloma is conflicting[9,12-14]. However, substantial benefit in renal outcomes has been shown in some retrospective studies that enrolled patients with circulating free light chains in the plasma or significant Bence-Jones proteinuria[15]. Moreover, there are three randomised controlled trials exploring this issue.

Zucchelli *et al.*[12] studied a group of 29 patients with multiple myeloma, acute renal failure (sCreat >5 mg/dL) and significant Bence-Jones proteinuria, 24 of whom required dialysis. The patients were randomly assigned to plasma exchange (five plasma exchange sessions on five consecutive days) together with glucocorticoids, cytotoxic drugs and haemodialysis (if needed), or to glucocorticoids, cytotoxic drugs and peritoneal dialysis (if needed). Of the plasma exchange group, 13 of 15 recovered renal function (most to a plasma creatinine concentration below 2.5 mg/dL), whereas improvement occurred in only 2 of 11 controls, with the majority requiring chronic dialysis. Patient survival was also improved in the plasmapheresis group (66% *vs.* 28%, $p< 0.01$).

In another trial[13] 21 myeloma patients were randomised: 11 were provided forced diuresis, chemotherapy and plasmapheresis (three plasma exchanges three times a week for 1-4 weeks) and the other 10 patients received equivalent therapy without plasmapheresis. No statistically significant differences in overall renal recovery or survival were noted. However, three out of seven patients requiring haemodialysis who were given plasma exchange improved, versus no improvement in any of the five dialysis patients in the control group. This study is limited by small sample size, variable duration of plasma exchange, the choice of more severely ill patients to perform plasmapheresis and exclusion of nonresponders to chemotherapy. Nevertheless, it outlines a role for plasmapheresis, which might enhance renal function in some cases.

These two studies led the scientific advisors of the International Myeloma foundation to formally endorse plasmapheresis use[9].

The third and largest randomised study[14], one involving 97 patients, failed to show any benefit. In this study, dialysis at baseline was less common than the previous studies, occurring in only 36% of control and 26% of plasmapheresis-receiving patients. Renal diagnosis was not confirmed in the majority of these patients, since biopsies were rarely performed. The results showed 69% of the controls and 58% of the plasmapheresis-receiving patients had an adverse outcome, which included death, dialysis dependence and estimate GFR< 30 mL/min/1,73m^2 at six months. Results were not statistically significant. Plasmapheresis appeared to be ineffective in myeloma patients with undifferentiated renal failure.

A 2010 review[15] of the seven most important studies in this field, including the three studies above, concluded that recovery from dialysis and improvement in renal function after plasmapheresis were reported in all studies. However, statistical significance in comparison with the control group was seen in only four studies. The varying outcomes of those studies could be explained by the fact that they used different protocols and were conducted over different periods of time. The significant advances through the last decades in the chemotherapeutic drugs used to treat multiple myeloma may also play a role. The role of kidney biopsy is also an important limitation that must be kept in mind in interpreting the results, as we saw in Clark's study[14].

Montseny *et al.*[5] reported on their histological study of 118 patients with monoclonal gammopathy that cast nephropathy was present in only 41%. The remaining 59% had AL amyloidosis, light chain deposit disease, chronic tubulointerstitial nephritis or cryoglobulinaemic kidney. According to this study and assuming similar proportions in other populations, only 41% of patients would theoretically benefit from plasma exchange. Indeed, as demonstrated in a recent review of 40 patients by Leung *et al.*[16], targeting patients with cast nephropathy and aggressively lowering the serum-free light chain value to < 50% helped to improve renal function in 78% of patients.

In our case report, the patient was similar to Zucchelli, Johnson and Leung's patients whose renal diagnosis of cast nephropathy had been confirmed, exactly the type of patient that, in our opinion, would benefit the most from plasmapheresis. We recommend plasmapheresis in cases with highly suggestive clinical presentations, based on high levels of free monoclonal light chains in the serum or urine even in the absence of a renal biopsy. In patients who

are unresponsive to plasmapheresis despite adequate suppression and removal of serum free light chains, a renal biopsy (if not yet performed) should be considered to investigate causes other than cast nephropathy[17].

It is reasonable to use partial replacement of the fluid removed with fresh frozen plasma (1 to 2 L at the end of the session), particularly in two circumstances: when plasmapheresis is started just after a kidney biopsy, due to higher risk of postbiopsy bleeding from pheresis-induced removal of coagulation factors and in the final treatment prior to catheter removal. In other every other treatment we recommend albumin as replacement fluid[17].

There are other extracorporeal removal techniques of light chains. There is a pilot study about extended haemodialysis using a high cut-off dialyser in patients with biopsy-proven myeloma kidney with acute renal failure dialysis-dependent. It showed that patients who receiving uninterrupted chemotherapy and extended High Cut-Off-Haemodialysis (HCO-HD) had sustained reductions in serum free light chain concentrations and recovered independent renal function. However, the role of FLC removal by HCO-HD still warrants further investigation as an adjunct to chemotherapy. Moreover, because plasma exchange remains a treatment option in this setting, a head-to-head trial of FLC removal by HD and plasma exchange would be interesting[18].

In our opinion the use of plasmapheresis in the treatment of cast nephropathy will remain a controversial issue for a long time since this is a relatively rare condition which implies a multicentre study and all the logistic problems it concerns. Furthermore, new and improved chemotherapeutic regimens are being developed all the time and that creates a large heterogeneity in comparing studies through times. We hope the results from an ongoing randomised European trial, MyEloma Renal Impairment Trial (MERIT)[15], will increase our knowledge.

Conflict of interest statement. None declared.

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