Lambda Light Chain Myeloma with Oliguric Cast Nephropathy and Remission with Bortezomib, Doxorubicin and Dexamethasone

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ABSTRACT

Cast nephropathy is one of the major causes of renal failure in patients with multiple myeloma resulting from precipitation of free light chains inside the tubules. Timely diagnosis and treatment confers a better prognosis though around 10% of patients with cast nephropathy remain dialysis dependent in spite of treatment.

We report the clinical course and outcome of a patient presenting with acute kidney injury and oliguria, preceded by acute gastroenteritis and intake of Chinese medications and dialysis dependent state for eight weeks. Kidney biopsy revealed cast nephropathy with lambda light chain restriction and severe tubular injury. Serum protein electrophoresis was normal with no "M spike" but serum free light chain ratio was altered with very high lambda and normal kappa light chain levels. Bone marrow biopsy showed >85% atypical plasma cells. Haemodialysis was continued and chemotherapy with bortezomib, doxorubicin and dexamethasone was started. Kidney function gradually improved with discontinuation of dialysis after 1 month and complete remission of acute kidney injury and myeloma in 4 months of chemotherapy.

Keywords: *acute kidney injury; bortezomib; cast nephropathy; multiple myeloma.*

INTRODUCTION

Acute Kidney Injury (AKI) of varying degree is present in 50% of patients with Multiple Myeloma (MM) at diagnosis with severe renal failure noted in around 10% of cases.[1-3] The prognosis of MM is directly affected by the presence and severity of AKI with median survival of <12 months in patients requiring dialysis at presentation.[4,5] The major pathology found in myeloma patients with azotemia is cast nephropathy characterized by the presence of fractured, waxy tubular casts formed by precipitation of excessively filtered free light chains with Tamm-Horsfall protein resulting in tubular obstruction, direct tubular injury and severe AKI.[6-8]

MM as the aetiology of severe unexplained AKI has been reported in several case series[5,9] and case reports.[10,11] Renal biopsies in these patients have revealed various morphological alterations including Light Chain Deposition Disease (LCDD), cast nephropathy and AL amyloidosis resulting from excessive production of monoclonal free light chains by myeloma cells.[12,13] Though the mortality of cast nephropathy needing dialysis is significantly high,[5,6] we report a case of

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severe AKI with oliguria due to lambda light chain cast nephropathy diagnosed on renal biopsy and complete remission of both AKI and myeloma on treatment with bortezomib, doxorubicin and dexamethasone.

CASE REPORT

A 53 year old male was admitted in Blue Cross Hospital with complaints of diarrhoea and vomiting for nine days followed by decreased urine output since five days. Patient admitted intake of traditional Chinese medicines for seven days. On examination patient was conscious, well oriented with puffy face, sub conjunctival haemorrhage and slight tenderness in epigastrium. Blood pressure (BP) was 130/70 mm of Hg, pulse 68/minute, temperature 98.6°F with no abnormalities in cardiovascular system and chest examination.

Investigations showed normal haemoglobin (12.8 gm / dl) and platelet (294000/mm^3), raised total leukocyte count (15600/mm^3), low sodium (116 mg/dl), high potassium (5.8 mg/dl) and severe renal failure (urea 163.7 mg/dl, creatinine 19 mg/dl). Routine urine examination showed no proteinuria and hematuria with WBC 10-12 per high power field.

Other investigations like liver function tests (bilirubin -total 0.9, direct 0.3, SGPT - 16.4, Alkaline phosphatase - 70), prothrombin time (14 min, INR 1.2), bleeding time (3 mins), clotting time (8 mins) were within normal limit. HBs Ag, HIV and Anti HCV were negative. X-ray chest revealed clear lung fields, cardiomegaly and old healed fracture of clavicle. Ultrasound abdomen showed normal sized kidneys (right kidney 12.3 cm and left kidney 11.9 cm) with grade 1 echogenicity. So the diagnosis was thought to be severe AKI due to acute gastroenteritis or leptospirosis with possibility of traditional medications as aggravating factor.

Blood culture, urine culture and Leptospira antibody tests were ordered. Antibiotic cover with intravenous Metronidazole and Ciprofloxacin was provided and haemodialysis started via subclavian catheter. Urine culture revealed growth of E. coli sensitive to Ciprofloxacin, Ofloxacin, Levofloxacin and Nitrofurantoin. Blood culture showed no growth and serology for Leptospira was negative. Echocardiography revealed mild concentric left ventricular hypertrophy with good systolic and diastolic function (Ejection Fraction 70%).

On third day of hospital admission, patient developed chest infection, prompting replacement of Ciprofloxacin with intravenous Imipenam with Cilastin, while continuing with thrice weekly haemodialysis. However leucocytosis and azotemia persisted with further worsening of clinical parameters. So, on second week serological investigations were ordered and intravenous Levofloxacin was added for coverage of atypical pneumonia that resulted in clinical improvement of chest findings and resolution of leucocytosis. But kidney function did not improve and serology revealed C3 hypocomplementemia with normal serum C4, P ANCA, C ANCA and negative anti GBM and ANA. In view of clinical and laboratory findings (renal dysfunction with persistent oligo-anuria and low serum complement level) possibility of proliferative glomerulonephritis was suspected and a kidney biopsy was performed three weeks after admission.

The histopathology showed normal glomeruli with no evidence of cellular proliferation, tuft necrosis or crescents. There was severe tubular injury with inspissation of many atypical "brittle" casts in lumina which exhibited "fracture planes", stained weakly with H&E and PAS stains, were non-congophilic and non-argyrophilic (Figure 1, 2). Immunofluorescence studies revealed minimal non-specific staining for IgM in glomeruli and intense 3+ staining for lambda light chains in intratubular casts with concurrent negativity for kappa light chains. A final diagnosis of severe tubular injury due to cast nephropathy with lambda light chain restriction was rendered. Further investigations including serum protein electrophoresis, serum free light chain ratio, serum immunoglobulin assay, B_2microglobulin and bone marrow aspiration and biopsy were done.

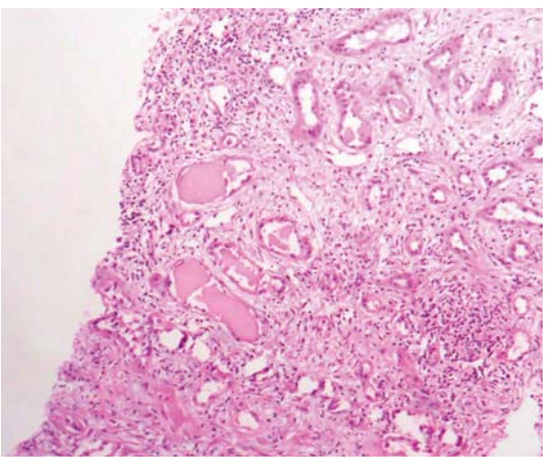

Figure 1. Photomicrograph of renal biopsy with medium magnification (20X H&E stain) showing intratubular myeloma casts with a fractured appearance with accompanying epithelial cell reaction, tubular injury and chronic tubulointerstitial nephritis.

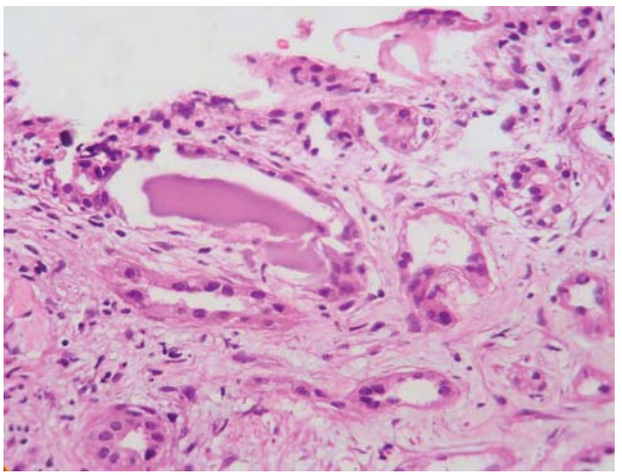

Figure 2. Photomicrograph of renal biopsy with high magnification (40X: H&E stain) of the atypical cast eliciting mild epithelial cell reaction of the tubular epithelial cells.

Though "M spike" in serum electrophoresis and lytic bone lesions were not observed, presence of >85% atypical plasma cells in bone marrow, very high serum lamda, free light chain 554.32 (5.71-26.3) mg/L, normal kappa, free light chain 12.16 (3.30-19.40) mg/L with altered kappa/lamda ratio 0.021(0.26 – 1.65) mg/L, high B_2microglobulin (17.8 mg/dl), reduced serum immunoglobulin IgG 573 (700-1600 mg/dl), IgM 25 (40-230 mg/dl) and IgA 23 (70-400 mg/dl) and renal biopsy findings confirmed the diagnosis of lamda light chain myeloma with cast nephropathy.

After a month of initiation of dialysis, chemotherapy with intravenous bortezomib 2 mg bolus (Day 1,4,8,11), doxorubicin 15 mg in 5% dextrose infusion in 24 hours (Day 1–4) and dexamethasone 40 mg Day 1 and 20 mg Day 2-4 of 21 days cycle, was administered. Within few days of initiation of chemotherapy urine output gradually increased to >1000 ml/day over two weeks however hemodialysis was continued due to persistence of azotemia. After initiation of second cycle of chemotherapy kidney functions improved further and dialysis was discontinued after two months of admission. Patient developed thrombocytopenia and neutropenia with chest infection after second cycle that was managed with platelet transfusion, intravenous antibiotics and deferred next chemotherapy by six weeks. Patient tolerated third cycle of chemotherapy well and investigation prior to fourth cycle revealed complete resolution of AKI with serum creatinine 1.2mg/dl and urea 16mg/dl and remission of MM with normal serum free light chains kappa – 19.6 mg/L and lamda – 13.46 mg/L and normal kappa/lamda ratio of 1.46.

DISCUSSION

Multiple myeloma, a plasma cell dyscrasia, results from excessive production of monoclonal immunoglobulin and/or light chains and is associated with increased predisposition to infections, spontaneous bone fractures and renal impairment. Diagnosis is made by presence of at least two out of four criteria - more than 20% plasma cells in bone marrow, radiological demonstration of lytic bone lesions, monoclonal band in serum and /or urine electrophoresis and Bence Jones proteinuria.[9] Though presence of renal impairment is not the diagnostic criteria, evaluation of unexplained AKI particularly in elderly patients has led to the diagnosis of MM with LCDD and cast nephropathy as the predominant pathology.[9-11]

In present case, kidney biopsy for unexplained severe AKI with persistent oligoanuria was performed and a diagnosis of cast nephropathy with lambda light chain restriction and severe tubular injury was obtained. Further investigations confirmed lambda light chain myeloma with raised serum free lambda light chains and >85% atypical plasma cells in bone marrow. Though a healed old clavicle fracture was found, there was no evidence of active lytic bone lesions and serum electrophoresis did not reveal M band.

The precipitation of casts in the distal tubules is predisposed by dehydration, sepsis, hypercalcemia and NSAIDS.[9] In the present case also, interaction of several factors including acute gastroenteritis, intake of traditional medicine, UTI and chest infection may have contributed to precipitation of casts in distal tubular lumina.

Severity of AKI and stage of myeloma at presentation are important predictors of survival in patients with MM. Studies have shown that majority of patients requiring dialysis at admission show little renal recovery with median survival of 4-10 months.[5,6] On the other hand there are reports of complete recovery of renal function in more than 1/3rd of patients with early initiation of dialysis and chemotherapy.[9]

Moreover, removal of excess light chains from circulation and choice of chemotherapy also govern the outcome. Plasma exchange has shown no benefit while high cut off haemodialysis with chemotherapy have resulted in remission of cast nephropathy.[14,15]

Among the chemotherapeutic regimens bortezomib with high dose dexamethasone,[16] melphelan/prednisolone,[17] and doxorubicin/dexamithasone,[18] have shown promising results and better renal recovery of AKI with or without dialysis. In this background, our patient was treated with bortezomib, doxorubicin and

dexamethasone. Patient's renal function showed gradual improvement after first cycle, dialysis independent after second cycle and complete remission of AKI and myeloma after third cycle of chemotherapy.

In conclusion, kidney biopsy for unexplained, dialysis dependent AKI had diagnosed multiple myeloma with cast nephropathy and complete remission AKI and myeloma had occurred with bortezomib, doxorubicin and dexamethasone.

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