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Case Report .

Acute Renal Failure Due to Cast Nephropathy without Multiple Myeloma

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ABSTRACT

We report a 64 year-man with acute renal failure on top of his chronic renal disease due to diffuse diabetic glomerulosclerosis. Serum creatinine had reached 600 umol/L from a baseline of 160 umol/L 4 months ago. Kidney biopsy revealed diffuse broad casts obstructing the distal tubules with interstitial fibrosis associated with cast's extravasation. The casts stained positive with kappa and not lambda indicating their monoclonal origin. The patient did not have evidence of lymphoprolifertive disease and myeloma in particular with normal skeletal survey and bone marrow trephine biopsy. Moreover, serum protein and urine electrophoresis failed to show monoclonal band. Only, direct serum testing for free light chain confirmed high Kappa and normal Lambda levels. The patient already had improved on corticosteroids and subsequently Melphalan was added. Serum creatinine decreased to 180 umol/L by the end of this 6-month treatment. The case illustrates a unique presentation of cast nephropathy without overt lymphoprolifertive disorder and with normal serum as well as urine protein electrophoresis. It emphasizes the need for kidney biopsy and/or direct measurement of serum free light chains for definitive diagnosis in such covert cases.

Key words: Cast Nephropathy, Light Chains Immunoglobulins, Multiple Myeloma, Renal Failure.

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INTRODUCTION

Renal failure (RF) is a frequent complication of multiple myeloma (MM) which may approach a prevalence of 43%. Moreover, it strongly affects the patient's survival with a 1 year survival of < 50% compared to 80% in those with serum creatinine < 1.5 umol/L.[1] Patients with MM usually present with bone aches and severe anemia. Diagnosis of MM is usually established by skeletal survey disclosing multiple lytic lesions as well as serum and/or urine showing monoclonal gammopathy.[2]

Significant proteinuria indicates glomerular disease with amyloidosis or light chain disease while RF, acute or chronic, indicates myeloma cast nephropathy (MCN). The latter is a tubulo-interstitial disorder related to precipitation of monoclonal light chain (LC) in the distal tubules.[3] Moreover, the proximal tubule can be affected by light chains, resulting in abnormalities such as renal tubular acidosis, hypouricemia, hypophosphatemia, aminoaciduria, renal phosphate wasting (e.g., Fanconi syndrome), and glycosuria.[4] In this case report we describe a unique presentation of a patient with acute RF due to MCN yet without such cardinal feature of MM.

CASE PRESENTATION

A 69 year-old, Kuwaiti man presented with mild left facial, upper limb and lower limbs weakness which was confirmed to be due to a recent ischemic infarct in the right basal ganglion. His serum creatinine had increased from 370 umol/L to 650 over a 2 weeks follow up. Review of his previous laboratory investigations revealed that his serum creatinine was 140 umol/L 4 months ago. The patient denied fever, shortness of breath, oedema, abdominal pain, skin rash and joint pains. His past medical history showed that he had type II diabetes mellitus for 10 years which was treated with Glimepiride 6 mg daily as well as he had hypertension for 2 years and was treated with amlodopine 10 mg daily. He denied any past medical history of surgery, allergy or chronic intake of medications especially non-steroidal anti-inflammatory ones. His physical examination was essentially unremarkable. Laboratory investigations showed normocytic normochromic anemia with hemoglobin at 120 g/L and high serum creatinine at 650 umol/L. Serum albumin, globulins, calcium and CPK were normal. Urine routine and microscopy was normal except for 1(+)

proteinuria and 10 RBCs/HPF. Ultrasound examination of the abdomen showed bilateral 10 cm kidneys with mildly echogenic cortex. After exclusion of infection, the patient was subjected to a kidney biopsy. On light microscopy, the latter showed adequate glomeruli with mild increase in mesangial matrix and interstitial expansion with fibrosis. Blood vessels showed mild hyalinization. The tubules contained extensive large hyaline casts (Fig.1). Many of those casts were seen in the interstitium and were surrounded by fibrosis and inflammatory reaction (Fig.2). Immunoperoxidase stains of those casts were positive for anti-Kappa light chain and negative for anti-Lambda (Fig.3).

Since this picture was compatible with cast nephropathy due to Kappa light chain the patient was treated with pulse Medrol (1g IV daily for 3 consecutive days) followed by Prednisone 1 mg/kg/day. Further testing of the patient with serum and urine protein electrophoresis failed to show monoclonal band (Fig.4). On the contrary, it had shown hypogammaglobulinemia with IgG at 7.1 g/L (N: 7.5-18), IgA at 0.5 g/L (N: 0.9-4.5) and IgM at 0.2 g/L (N: 0.6-2.5). Skeletal survey did not show any lytic lesion. Bone marrow aspirates and trephine biopsy failed to show increase in plasma cells in bone marrow or lymphoprolifertive disorders. Moreover, immunophenotyping testing failed to show abnormality. However, direct serum testing for light chain immunoglobulins confirmed a very high level of Kappa at 2571 mg/L while Lambda was just 21 mg/L i.e. with K/L ratio at > 122. With his initial corticosteroid therapy, his serum creatinine had decreased by an average of 100 umol/month. Melphalan was added 1 week after his initial evaluation i.e. after documenting his disease by kidney biopsy.

The latter permitted gradual reduction of his high corticosteroid dose and eased the control of his severe steroid-induced hyperglycemia. Serum creatinine had decreased to 180 umol/L by the end of this 6-month treatment and his serum free Kappa light chain level had decreased to 71 mg/L.

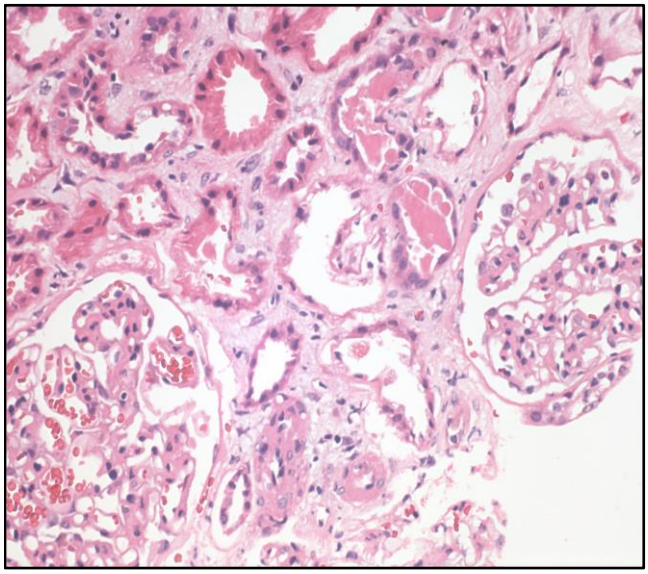

Figure 1: Show mesangial matrix increase with scattered broad casts in tubules with interstitial fibrosis. (H&E X100)

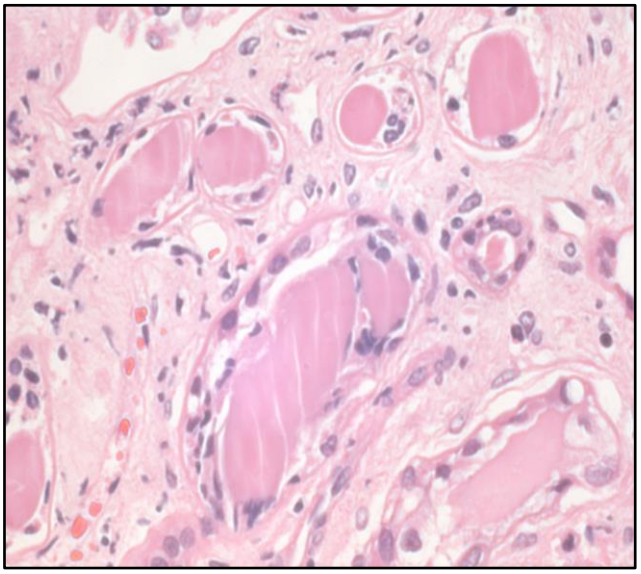

Figure 2: Photomicrograph of kidney biopsy of the patient showing casts in tubules surrounded by inflammatory cell and early fibrosis (H&E X200).

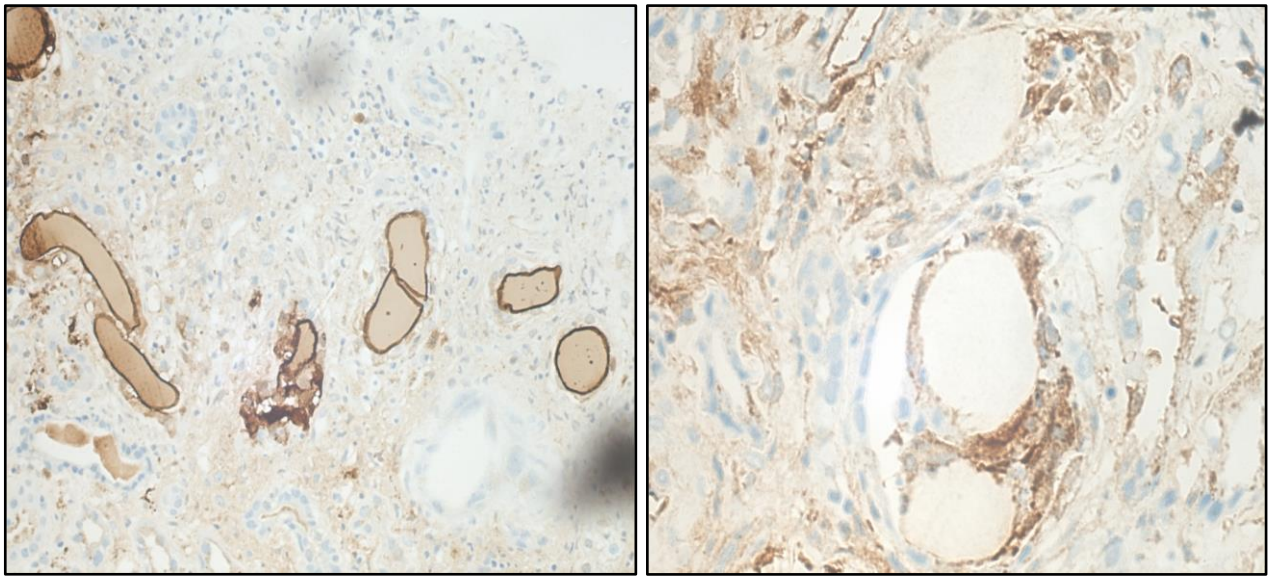

Figure 3: Immunoperoxidase stain of the tubular casts showing lack of stain for Lambda (A) and positive stain for Kappa (B).

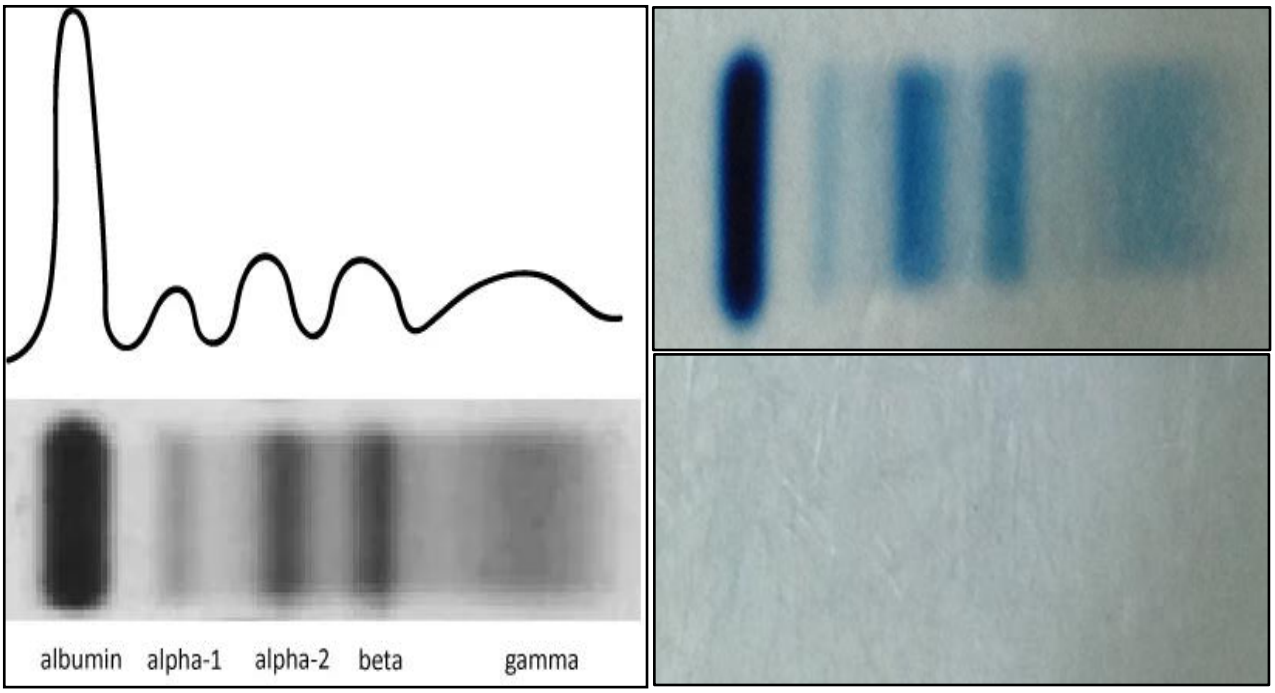

Figure 4: Automated microgel electrophoresis (High resolution gel) of normal control (A), Patient's serum (B) and patient's urine (C). Note absence of monoclonal band in the patient's serum and urine.

DISCUSSION

Our patients did not have the classic features MM viz. bone aches, anemia, hypercalcemia, lytic bone lesions, proximal tubular defect, monoclonal gammopathy and his bone marrow biopsy as well as his immunopheotyping was normal. Diagnosis was established, primarily, by kidney biopsy and immunoperoxidase stains. Subsequently, high levels of Kappa light chain confirmed the diagnosis. This unique presentation indicates a limited sensitivity of the clinical features of and the standard tests in diagnosis of MM. RF associated with MCN has been described with monoclonal light chains in lymphoma[5], Waldenström macroglobulinemia[6] and with polyclonal light chains due to proximal tubular damage induced by Rifampcin[7], combination of Tacrolimus and Rapamycin[8] as well as in patients with acinar cell carcinoma of the pancreas.[9] Our patient did not have evidence of lymphoprolifertive disease by clinical and laboratory testing as well as immunophenotyping. Moreover, he did not have previous exposure to such drugs and his immunoperoxidase stains demonstrated monoclonal casts. The SFLC assay is very useful in the diagnosis of MCN. The SFLC assay quantities the concentration of circulating kappa and lambda (unbound) FLCs. The normal serum free kappa to lambda ratio is 0.26 to 1.65 in patients without renal failure. Elevated FLC in association with an abnormal SFLC ratio indicates a monoclonal plasma cell proliferative process. The SFLC assay is more sensitive than the serum and urine protein electrophoresis for detecting monoclonal proteins and moreover, suggestive of diagnosis if levels > 1500 mg/L and is extremely unlikely with levels < 750 mg/L.[10,11] By definition, the diagnosis of MCN indicates the presence of MM i.e. it is considered a "MM-defining event".[2] MCN is caused by large amount of monoclonal free light chain which can cause RF by intratubular cast formation and/or direct tubular toxicity.[12,13] Volume depletion contributes by slowing the flow within the tubules and by promoting the formation of large aggregates. Other factors that may promote intratubular cast formation include loop diuretics, increased urinary calcium as a result of hypercalcemia, radiocontrast media, and Nonsteroidal anti-inflammatory drugs.[12] Early diagnosis and rapid lowering of levels of light chain proteins are essential in treatment of MCN since untreated MM with RF has a grim prognosis and with limited survival of 4 months only.[14] Moreover, even the response to therapy is another major prognostic value.[15] Lowering of SFLCs can be achieved with multiple extracorporeal dialysis techniques viz. hemodialysis, extended high cutoff on-line hemodiafilteration, theralite dialyzers and plasmaphoresis.[16] Unfortunately the results of randomized controlled studies were controversial.[17] Chemotherapy remains the most effective method not only for arresting the disease progression but also in reducing SFLCs as in our patient. New biological agents with less immediate and long-term side effects such Boretzomib are being tried with an encouraging success.[18]

In conclusion, patients above the age of 40 years with unexplained acute RF that occurred over a 6-months period and with bland urine sediment should be screened for MCN. Kidney biopsy and/or direct measurement of serum free light chains are the most reliable mean of diagnosis if clinical features are atypical or standard testing by serum and urine electrophoresis as well as skeletal survey, bone marrow is negative.

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