

Delayed Diagnosis of Multiple Myeloma Presenting with Renal Failure

Afeaje B. Olorokó and Evelyn I. Unuigbo

Department of Internal Medicine, University of Benin, Benin City

ABSTRACT

Kidney disease is one of the numerous complications of multiple myeloma, arising either as a result of the tumor, its product or response of the host to the proliferation of plasma cells. It is a common feature of multiple myeloma.

Presentation of kidney disease in multiple myeloma varies, just as the pathogenic mechanisms in multiple myeloma that give rise to kidney disease directly or indirectly are varied.

We report the case of a 64 year retired school teacher, who presented with features suggestive of pre-renal acute kidney injury and preceding lumbar spondylosis in which the diagnosis of multiple myeloma was delayed.

Keywords: *Multiple myeloma, acute kidney injury, late diagnosis*

INTRODUCTION

Multiple Myeloma is a malignant proliferation of plasma cells originating from a single clone [1]. It accounts for 10% of hematologic cancer second only to non-Hodgkins lymphoma [2,3].

In about 30% of cases, the diagnosis is made during investigation for an unrelated problem. Common clinical presentations include bone pains seen in about 70% of cases at presentation, anemia, bleeding, pathologic fractures and renal failure [3,4].

Renal failure is seen in about 20% of cases, while some degree of renal impairment is observed at some point in the natural history of nearly all cases

of myeloma. When severe, it is associated with significant mortality [5].

CASE REPORT

Mrs. OB, a 64-year old retired teacher presented at the accident and emergency unit with a one-week history of low back pain, fever, generalized body weakness and a two-day history of passage of loose stools and vomiting.

Low back pain was gradual in onset, initially moderate in intensity but progressed with associated difficulty walking and bending over. Pain was however non-radiating. There were no associated pains in other joints. No history of trauma prior to onset. There was a history of recurrence of similar pain in the past.

Generalized body weakness resulted in inability to carry out her daily chores but was not associated with dizziness or fainting spells.

Fever was low grade, not associated with chills or rigors. She had increased urinary frequency with mild intermittent lower abdominal pain. Two days prior to presentation she had several episodes of vomiting and loose stools. Stools were non-mucoid, non- bloody with associated lower abdominal pain. There was a history of reduced urinary output following diarrhea and vomiting.

She was diagnosed hypertensive 8 years prior to this index presentation but she was not adherent with prescribed anti-hypertensives. She was being managed for lumbar spondylosis by an orthopedic surgeon 3 years before this index illness

Corresponding author: *Afeaje Benedicta Olorokó*, University of Benin Teaching Hospital Benin City *E-mail:* afeaje24@gmail.com

and had being on intermittent use of non-steroidal anti-inflammatory drugs for treatment.

Physical examination revealed a middle aged woman, who was dehydrated, pale, anicteric, afebrile and had no peripheral edema.

Her pulse rate was 84 beats per minute, regular, normal volume; blood pressure was 120/60mmHg supine, jugular venous pressure was not elevated and apex beat was not localized due to a thickened anterior chest wall. Heart sounds were one and two only.

She had a respiratory rate of 20 cycles per minute, but her chest was clinically clear.

She had tenderness in the right iliac fossa and supra-pubic regions.

Her central nervous system was essentially normal with no asterixis.

Urinalysis revealed turbid urine with 3⁺⁺⁺ proteinuria, specific gravity was 1.015.

An initial assessment of an acute kidney injury precipitated by gastroenteritis and a urinary tract infection in a patient with Hypertension and Lumbar spondylosis was made. Investigations and results are shown in table 1

Table 1: Investigations and results on admission

PARAMETER	RESULTS
MSU/ MCS δ	Pus cells 1-2hpf Growth of E. coli sensitive to cefuroxime, imipinem and ciprofloxacin
FBC	
Hematocrit δ	20.6%
White blood cells	9,700 cells/ml
Mean corpuscular volume δ	65.8fl
Platelets δ	109,000 cells/ ml
Blood chemistry	
Serum Urea δ	176 mg/dl
Serum Creatinine δ	2.8 mg/dl
Potassium	3.7 mmol/L
Sodium	135 mmol/L
Bicarbonate δ	9 mmol/L
Chloride	101 mmol/L
Serum calcium	8.9 mg/dl
Serum phosphate δ	6.9mg/dl
Estimated GFR	21mls/min
Renal ultrasound scan	
Right kidney	10.04cm by 3.87 cm
Left kidney	11.11cm by 5.5cm δ Increased echogenicity, some loss of corticomedullary differentiation

MSU/MCS - Mid stream urine microscopy, culture and sensitivity, FBC –Full blood count, GFR- Glomerular filtration rate.

δ - Abnormal results

She was commenced on intravenous fluid normal saline to alternate with 5% dextrose saline 500mls 6hourly, intravenous ciprofloxacin 200mg 12hourly and tramadol 50mg orally twice daily. She was also commenced on subcutaneous erythropoietin 4,000IU twice weekly and injection iron sucrose. Antihypertensives were withheld.

She was noticed to have become anuric passing about 10mls of urine in the first 12 hours on admission. Due to persistent anuria despite rehydration and cessation of gastroenteritis, deranged levels of serum urea and creatinine she was

commenced on haemodialysis. She had a unit of blood transfused prior to dialysis.

She had six sessions of haemodialysis on alternate days but remained anuric. During this time hematocrit ranged between 17 -21% and she was transfused with 4 units of blood.

With the presence of anemia, thrombocytopenia, worsening renal function the possibility of a connective tissue disease was considered and further investigations were carried out as shown in table 2.

Table 2: Investigations and results 3 weeks on admission

PARAMETERS	RESULTS
Erythrocyte sedimentation rate (ESR)	3mm/hr
C- Reactive protein ^δ	40.1 mg/L
Anti-nuclear Antibody	Negative
Peri-nuclear anti-neutrophil cytoplasmic antibody(p-ANCA)	Negative
Cytoplasmic anti-neutrophil cytoplasmic antibody(c-ANCA)	Negative

δ Deranged laboratory parameters

On further review the waist pain had worsened, this warranted further investigations which included a lumbosacral spine x-ray that revealed collapse of the first lumbar vertebra and partial collapse of the 11th and 12th thoracic vertebrae associated with significant osteoporosis. Following these radiological findings, a diagnosis of multiple myeloma was entertained and the Haematology team was invited for further evaluation.

Bone marrow aspirate and biopsy done showed mixed deficiency anemia with dilute cellular marrow, a reduced myeloid / erythroid ratio with relatively suppressed erythropoiesis, megaloblasts and micro- normoblast, suppressed myelopoiesis with sequential and occasional megakaryocytes seen. Plasma cells were increased to more than 30% with occasional flaring forms and a few bi-nucleated forms. There was bone marrow plasmacytosis.

Further investigations done showed increased serum lactate dehydrogenase of 660.3IU, positive Bence Jones proteinuria and serum protein electrophoresis that showed a thickening of the beta IgA region suggestive of IgA monoclonal gammopathy.

Her hematocrit was noted to be on the decline despite use of erythropoietin and iron sucrose and ranged between 16 -25%; she was transfused with another 3 pints of whole blood.

She was billed to be commenced on Bortezomib and dexamethasone, unfortunately, an industrial action militated against her getting regular access to hemodialysis and commencement of above drugs as planned by the hematologist; she eventually succumbed to acute pulmonary edema.

DISCUSSION

Multiple Myeloma (MM) is one of the causes of kidney disease and is often associated with a high mortality rate [4]. Age at presentation is usually greater than 60 years; with a minority of patients less than 40 years old and can occasionally be seen in late teens or 20s [4]. The index patient was aged 64 years, an age at high risk of MM.

Renal insufficiency is seen in about 20% of multiple myeloma cases [6], arising from numerous pathogenic mechanisms [4] which include direct toxic effect of the light chains, volume depletion, sepsis,

monoclonal immunoglobulin deposition, medication toxicity, nephrocalcinosis from hypercalcemia, amyloidosis and hyperviscosity. A manifestation of the direct toxic effects of the abnormal light chains is cast nephropathy which is also referred to as myeloma kidneys. In cast nephropathy, intratubular casts and crystals are formed from the filtered monoclonal light chains, obstructing distal renal tubules; sometimes of sudden onset and simultaneously resulting in tubulointerstitial nephritis as obstructed tubules rupture [7]. Severe kidney disease in a MM patient is most commonly due to cast nephropathy often preceded by a trigger which in this case may have been the gastroenteritis [8]. This in retrospect may have contributed to the anuria observed in our patient, as this in addition to the gastroenteritis could have led to volume depletion.

MM patients can present subtly as anaemia, minimal proteinuria or acutely as AKI dependent on dialysis. Anemia, a hallmark of MM is seen in 75% of cases, our patient had persistent anemia necessitating as much as 7 units of blood despite administration of erythropoietin.

The CRAB criteria [2] used in diagnosing active multiple myeloma includes hyperCalcemia, Renal failure, Anemia, Bone (lytic or osteopenic) lesions; all of these except hypercalcemia were present in our patient.

The diagnosis of a smoldering disease is based on [9] M-protein in serum (IgG ≥ 3 g/dL, IgA > 1 g/Dl) or Bence-Jones protein > 1 g/24h and/or bone marrow clonal plasma cells $\geq 10\%$.

The diagnosis of MM may sometimes be delayed due to the absence of clinical features specific to the disease and the absence of the myeloma cells on blood films and complete blood counts [10]. In the elderly, the presence of co-morbidities may also obscure the diagnosis of MM induced kidney disease. In our patient previous diagnosis of lumbar spondylosis and hypertension (with the possibility of hypertensive nephrosclerosis) may have obscured or delayed the diagnosis of MM. Absence of laboratory results to support the diagnosis of MM also contributed to delay in diagnosis of MM in this patient. For example, serum calcium and erythrocyte sedimentation rate were within normal range on admission for our patient.

Management involves optimization of hemodynamic status, rehydrating where necessary, and avoidance of loop diuretics (which can accelerate

formation of casts), avoidance of angiotensin converting enzyme inhibitor, non-steroidal anti-inflammatory drugs and use of contrast media.

The treatment options available for myeloma-associated kidney disease include chemotherapy such as the proteasome inhibitor e.g. bortezomib in combination with thalidomide or dexamethasone. This has been shown to extend survival for even patients dependent on dialysis [11].

Other treatment options include stem cell transplantation, plasmapheresis and kidney transplantation. Although the presence of renal disease and in particular the terminal stages appear to worsen prognosis of MM, early diagnosis of the disease and initiation of treatment is associated with improved survival [12].

In conclusion, delayed diagnosis of MM related kidney disease in our patient was due to earlier diagnosis of Lumbar Spondylosis that could have masked bone pains of MM as well as lack of laboratory support for diagnosis. The incessant industrial actions in our health care system deprived our patient access to treatment that led to her eventual death.

A high index of suspicion is necessary to be able to pick up cases of MM so as to avoid developing late stages of renal disease that are financially difficult to cope with.

REFERENCES

1. Hideshima T et al: Understanding multiple myeloma pathogenesis in the bone marrow to identify new therapeutic targets. *Nat Rev Cancer* 2007; 7:585.
2. Caers J, Vande broek I, De Raeve H, Michaux L, Trullemans F, Schots R, et al. Multiple myeloma—an update on diagnosis and treatment. *Eur J Haematol.* 2008 Nov. 81(5):329-43.
3. Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. *Leukemia.* 2009 Jan. 23(1):3-9.
4. Eliot H, Helmut R, Jacob L, Paul R. kidney disease and multiple myeloma. *Clin J Am Soc Nephrol*, 2013. doi: 10.2215
5. Knudsen LM, Hippe E, Hjorth M, Holmberg E, Westin J. The Nordic Myeloma Study Group Renal function in newly diagnosed

- multiple myeloma—a demographic study of 1353 patients. *Eur J Haematol* 1994, 53: 207–212,
6. Bladé J, Fernández-Llama P, Bosch F, Montolíu J, Lens XM, Montoto S, et al. Renal failure in multiple myeloma: presenting features and predictors of outcome in 94 patients from a single institution. *Arch Intern Med*. 1998 Sep 28. 158(17):1889-93
 7. Herrera GA, Joseph L, Gu X, Hough A, Barlogie B: Renal pathologic spectrum in an autopsy series of patients with plasma cell dyscrasia. *Arch Pathol Lab Med* 128: 875–879, 2004
 8. MA Dimopoulos, E Terpos, A Chanan-Khan, et al: Renal impairment in patients with multiple myeloma: A consensus statement on behalf of the International Myeloma Working Group *J Clin Oncol* 2010,28: 4976–4984.
 9. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology, Multiple Myeloma. Version 3.2018—November 22.
 10. OP Kapoor. Multiple Myeloma - A ‘Cancer’ which can be Easily Missed by Family Physicians. *Bombay Hospital Journal*, 2010; Vol. 52(1)85.
 11. Torra R, Bladé J, Cases A, López-Pedret J, Montserrat E, Rozman C, Revert L. Patients with multiple myeloma requiring long-term dialysis: Presenting features, response to therapy, and outcome in a series of 20 cases. *Br J Haematol* 1995, 91: 854–859.
 12. Alexanian R, Barlogie B, Dixon D. Renal failure in Multiple Myeloma: pathogenesis and prognostic implications. *Arch Intern Med*. 1990;150:1693-1695