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CASE REPORT

Light chain multiple myeloma: an evaluation of its biochemical investigations

Siti Yazmin ZAHARI SHAM *BM, MPath*, Subashini C. THAMBIAH *MBBS, MPath*, Intan Nureslyna SAMSUDIN *MBBch Bao, MPath* and Say Min LIM *MD*

Department of Pathology, Faculty of Medicine and Health Sciences, University Putra Malaysia

Abstract

Multiple myeloma is a type of plasma cell dyscrasia, characterised by presence of paraprotein or monoclonal (M)-protein in serum or urine. The M-protein may consist of an intact immunoglobulin, the heavy chain only or the light chain only. The latter, designated as light chain multiple myeloma (LCMM) makes up almost 20% of myelomas. Clinical manifestation is often heralded by hyper*c*alcaemia, *r*enal impairment, normocytic normochromic *a*naemia and *b*one lesions, reflecting end-organ damage, collectively known as the acronym *CRAB*. In particular, free light chain nephrotoxicity accounts for the high prevalence of renal impairment seen in LCMM. This case illustrates a typical presentation of LCMM with focal discussion on its initial and diagnostic, as well as prognostic biochemical investigations.

Keywords: light chain multiple myeloma, diagnosis, prognosis, biochemical investigations

INTRODUCTION

Multiple myeloma is a type of plasma cell dyscrasia, characterised by the presence of paraprotein or monoclonal (M)-protein in serum or urine.[1] The M-protein may be an intact immunoglobulin, the heavy or light chain only. The latter, designated as light chain multiple myeloma (LCMM) makes up almost 20% of myelomas.[1] We report a case of LCMM in an elderly gentleman focusing on its biochemical tests.

CASE REPORT

A previously healthy 64-year-old Chinese man presented with worsening back pain and bilateral lower limb numbness. He also complained of poor appetite and lethargy. Examination revealed a kyphotic posture with lumbar tenderness and a positive sciatic test. An L4/L5 compression fracture was later confirmed radiologically. Findings of hyper*c*alcaemia, *r*enal impairment, normocytic normochromic *a*naemia and *b*one lesions, reflecting end-organ damage, collectively known as the acronym *CRAB*, were strongly suggestive of multiple myeloma (Table 1). Serum and urine protein electrophoreses (SPE and UPE, respectively) showed paraproteinaemia (Fig. 1). Absence of heavy chain was confirmed by incorporating extensive immunofixation electrophoresis (IFE) using anti G, A, M, D and E antisera (Fig. 2). A diagnosis of kappa light chain disease was made and further supported by the markedly abnormal kappa:lambda (κ:λ) ratio of 876.54 by means of serum free light chain (FLC) assay.

DISCUSSION

Clinically, this patient's presentation with CRAB criteria of hypercalcaemia, renal insufficiency, anaemia and bone lesion was classical of multiple myeloma. Bone pathology is commonly seen in up to 70% of patients.[2] Suppression of normal red blood cell production, compounded by reduced erythropoietin production in renal impairment, gives rise to normocytic normochromic anaemia in more than 60% of patients.[2] Hypercalcaemia is common and partly accounts for non-specific symptoms such as lethargy and anorexia, seen in this patient.

Initial biochemical investigations

On admission, raised creatinine:urea ratio (Table 1) was suggestive of intrinsic rather than

Address for correspondence: Siti Yazmin Zahari Sham, Department of Pathology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400, Serdang, Selangor. Email: sitiyazmin@upm.edu.my

TABLE 1: Laboratory results

Test	Result	Reference range (unit)
Haemoglobin	10.1	11.5 - 15.5 g/dL
White Blood Cell	9.9	4 - 11.0 X 10^9/L
Platelet	335	150 - 400 X 10^9/L
Mean Corpuscular Volume	82	80 - 95 fL
Mean Corpuscular Haemoglobin	29.2	27 - 34 pg
Urea	6.1	2.5 - 7.2 mmol/L
Sodium	144	136 - 145 mmol/L
Potassium	5.0	3.5 - 5.1 mmol/L
Creatinine	156	53 - 97 umol/L
Calcium	3.41	2.14 - 2.58 mmol/L
Adjusted calcium	3.51	
Phosphate	1.03	0.81 - 1.45 mmol/L
Total Protein	52	60 – 83 g/L
Albumin	35	40 – 49 g/L
Total Bilirubin	11	< 17 umol/L
Alkaline Phosphatase (ALP)	140	5 – 141 U/L
Alanine Transferase (ALT)	22	5 – 33 U/L
Intact Parathyroid hormone (iPTH)	1.86	1.3 - 7.6 pmol/L
Erythrocytes sedimentation rate (ESR)	48	1-15 mm/hr
Beta-2-microglobulin (B2M)	6.15	1.1 - 2.6 mg/L
Kappa Free Light Chain (FLC)	7100	3.3 - 19.4 mg/L
Lambda FLC	8.1	5.7 - 26.3 mg/L
Kappa:Lambda ratio (κ:λ)	876.54	0.26 - 1.65

pre-renal impairment. Despite this, he was noted to be hypercalcaemic with adjusted serum calcium of 3.51 mmol/L. Hypercalcaemia in the presence of renal impairment is suggestive of malignancy, being most likely driven by parathyroid hormone-related peptide (PTH-rP).[3] PTH-rP increases both bone resorption and renal reabsorption of calcium whilst its phosphaturic effect results in hypophosphataemia. Thus in this patient, an inappropriately normal serum phosphate was in keeping with renal impairment as was a high-normal serum potassium (Table 1). In the presence of hypercalcaemia, serum iPTH is normally suppressed. However, his iPTH was normal. Interestingly, it is said that the most likely cause of hypercalcaemia in the setting of malignancy with increased or normal PTH concentration is co-existing hyperparathyroidism.[3] However, this was not further investigated for in this patient.

Multiple myeloma is more commonly associated with hyperproteinaemia with a reversed albumin:globulin ratio. Thus in this patient, hypoproteinaemia may reflect poor nutritional intake. Hypoalbuminaemia, as in this patient, is commonly seen in advanced stage of multiple myeloma, reflecting chronic disease. The high-normal alkaline phosphatase (ALP) was most likely bone in origin, given the presence of pathological fracture and a normal level of liver transaminase (ALT).

Diagnostic biochemical investigations

Biochemical diagnosis of multiple myeloma relies heavily on the detection of paraprotein. This has been traditionally achieved by SPE and UPE.[4] Recently, serum FLC assay has been incorporated in the recommended biochemical investigations of multiple myeloma, particularly LCMM and other light chain diseases.[4]

His SPE (Fig. 1) which was confirmed by an extensive IFE (Fig. 2) showed kappa light chain with no immunoparesis. His UPE (Fig. 1) and uIFE (Fig. 2) showed kappa light chain paraproteinuria. In support, measurement of his serum FLC showed a markedly increased level of kappa FLC and κ:λ ratio (Table 1).

LCMM occurs in up to 50% of patients with significant renal impairment.[5] FLCs are directly toxic to the proximal tubular cells, causing progressive cell death[6], inducing tubular dysfunction (Fanconi syndrome) or cast nephropathy ("myeloma kidney").[7] In addition, FLC may also lead to amyloidosis, which was

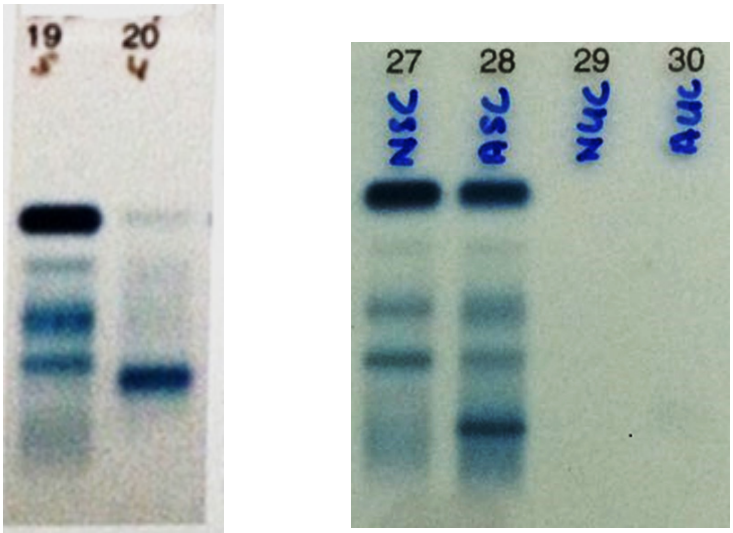

FIG. 1: Patient's protein electrophoresis
19: Serum (S)
20: Urine (U)
27: Normal serum control (NSU)
28: Abnormal serum control (ASU)
29: Normal urine control (NUC)
30: Abnormal urine control (AUC)

one of the conditions to rule out in this case. However, amyloidosis is more commonly associated with λ FLC chains, while myeloma with κ FLCs.[7]

Acknowledging the limitations of serum creatinine by non-renal factors such as age and muscle mass, the international guideline has moved away from a fixed value of serum creatinine of >173 mmol/L to using glomerular filtration rate (GFR), measured or estimated, in defining renal impairment in myeloma.[8] In the light of new evidence, it has now incorporated

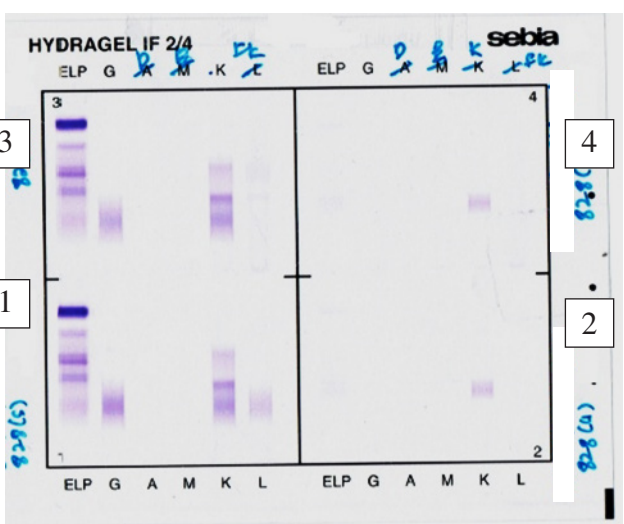

FIG. 2: Patient's serum and urine IFE
1 & 3: Serum
2 & 4: Urine
1 & 2: IFE with G, A, M, kappa and lambda antisera
3 & 4: IFE with G, D, E, kappa and free kappa antisera

levels of serum FLC in redefining myeloma kidney as part of the *CRAB* criteria.[8] Patients with myeloma kidney typically have baseline serum FLC concentrations exceeding 500 mg/L.[9] Serum FLC of >1500 mg/L, which is presumptive of light chain cast nephropathy, is regarded as myeloma-defining event.[8] Renal biopsy is recommended to clarify the underlying cast nephropathy particularly if serum FLC is less than 500 mg/L[8], which was not the case in this patient. Accordingly, in this case, although his serum creatinine was less than 173 mmol/L, his serum κ FLC level of >1500 mg/L (7100 mg/L) (Table 1), may be taken as a presumptive diagnosis of light chain cast nephropathy, which occurs exclusively in myeloma kidney.

Alternatively, the underlying renal pathology may be inferred to a certain extent from the degree and pattern of proteinuria seen on densitometry and UPE, respectively. Glomerular proteinuria, indicating an underlying glomerular damage such as glomerulonephritis typically presents as gross proteinuria of >3.5 g/day and a pattern of albuminuria on UPE.[7,10] Tubular damage, such as Fanconi syndrome, is suggestive by proteinuria of 1-3 g/day and a more generalised pattern of proteinuria on UPE.[7,10] In this case, although proteinuria of 1.22g/L was detected (details of his densitometry was however not shown), absence of 24-hour urine volume hinders estimation of the degree of proteinuria. However, a generalised pattern of proteinuria seen on his UPE was supportive of tubular damage, in keeping with the presumptive diagnosis of light chain-cast nephropathy.

Prognostic biochemical investigations

Beta-2-microglobulin (B2M) is a prognostic marker whose raised level reflects high tumour burden and reduced renal function.[11] Together with serum albumin, serum B2M is incorporated in the International Staging System (ISS).[11] Unfortunately, his serum B2M of 6.15 mg/L (>5.5 mg/L) would classify this patient as Stage 3 with an estimated median overall survival of 29 months.[11] Lactate dehydrogenase (LDH), a glycolytic enzyme, is another recognised prognostic marker in many haematological malignancies, including multiple myeloma.[12] Recently, the Revised-International Staging System has been established incorporating the existing ISS, LDH and chromosomal abnormalities to further improve patient risk stratification with better prediction of overall survival rate.[12] However, LDH and chromosomal studies were not done in this patient. These tests would probably be done eventually as he was later transferred to a reference hospital.

Conclusion

In conclusion, despite the emergence of newer tests in multiple myeloma, conventional tests may remain relevant with limited yet useful information still inferable from them. Such conventional tests encompass both initial and diagnostic investigations, such as serum creatinine and UPE, respectively, with their newer counterpart of serum FLC assay. On the other hand, a conventional marker such as LDH is re-emerging as part of a newly revised staging system.

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REFERENCES

1. Sirohi B, Powles R. Multiple myeloma. Lancet. 2004; 363: 875-87.
2. Barber FD, Mullen EC. Multiple myeloma: the role of the primary care nurse practitioner. J Nurse Pract. 2017; 13: 328-35.
3. Clines GA, Guise TA. Hypercalcaemia of malignancy and basic research on mechanisms responsible for osteolytic and osteoblastic metastasis to bone. Endocr Relat Cancer. 2005; 12: 549-83.
4. Dispenzieri A, Kyle R, Merlini G, *et al*. International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders. Leukemia. 2009; 23: 215-24.
5. Corso A, Zappasodi P, Lazzarino M. Urinary proteins and renal dysfunction in patients with multiple myeloma. Biomed Pharmacother. 2002; 56: 139-43.
6. Clark AD, Shetty A, Soutar R. Renal failure and multiple myeloma: pathogenesis and treatment of renal failure and management of underlying myeloma. Blood Rev. 1999; 13: 79-90.
7. Levinson SS, Keren DF. Free light chains of immunoglobulins: clinical laboratory analysis. Clin Chem. 1994; 40: 1869-78.
8. Rajkumar SV, Dimopoulos MA, Palumbo A, *et al*. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014; 15: e538–48.
9. Jenner E. Serum free light chains in clinical laboratory diagnostics. Clin Chim Acta. 2014; 27: 15-20.
10. Tate JR, Graziani MS, Mollee P, Merlini G. Protein electrophoresis and serum free light chains in the diagnosis and monitoring of plasma cell disorders:

laboratory testing and current controversies. Clin Chem Lab Med. 2016; 54: 899-905.
11. Greipp PR, San Miguel J, Durie BG, *et al*. International staging system for multiple myeloma. J Clin Oncol. 2005; 23: 3412-20.
12. Palumbo A, Avet-Loiseau H, Oliva S, *et al*. Revised international staging system for multiple myeloma: a report from International Myeloma Working Group. J Clin Oncol. 2015; 33: 2863-69.