Unusual manifestation of monoclonal gammopathy of undetermined significance: a false serum creatinine elevation

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Abstract

A 72-year-old Japanese man with diabetes mellitus and hypertension presented with an acutely elevated serum creatinine level, from 1.02 to 4.13 mg/dL over 2 months as measured by the enzymatic method by pure-auto S CRE-N[®]. Renal biopsy could not identify the etiology of the elevating sCr. However, an elevated total protein level (8.2 g/dL) and lowering of the BUN and sCr ratio from 14.5 to 2.7 were found, and bone marrow biopsy showed less than 10% lymphoplasmacytic infiltration, compatible with monoclonal gammopathy of undetermined significance. The diagnosis of a false serum creatinine elevation due to monoclonal gammopathy of undetermined significance was confirmed with the serum cystatin C level at 1.05 mg/dL and the creatinine level of 0.97 mg/dL using Shikarikiid-S CRE[®] method. Although cases of monoclonal gammopathy of undetermined significance with a false serum creatinine elevation as an initial presentation are rare, this condition should be considered in patients with paraproteinemia; measuring the renal function using cystatin C is important in such patients.

Keywords Monoclonal gammopathy · Paraproteinemia · Cystatin C · Creatinine

Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant clonal plasma cell disorder characterized by a serum monoclonal protein (M protein) concentration lower than 3 g/dL; less than 10% clonal plasma cells in the bone marrow; and absence of lytic bone lesions, anemia, hypercalcemia, and renal insufficiency that are related to the M protein [1–3]. It is usually diagnosed incidentally on laboratory testing [4]; however, cases of MGUS with a false serum creatinine elevation as an initial presentation are rare. Here, we report a rare case of a 72-year-old Japanese man with MGUS who initially presented with a falsely elevated serum creatinine level. Measurement of the

cystatin C level proved to be useful in diagnosing this condition. In addition, we reviewed the literature of such cases.

Case report

A 72-year-old Japanese man was referred to our medical center with abrupt elevation of his serum creatinine (sCr) level from to 4.13 mg/dL over 2 months. There was no complaint of back pain, weakness, or fatigue. He had diabetes mellitus and hypertension, and was taking amlodipine, candesartan, and metformin. He had no history of any drug abuse, known allergies, or smoking; he only occasionally drank alcohol. He had no family history of hematological cancers or kidney disease. On examination, his respiratory rate was 12 breaths per minute, heart rate was 64 beats per minute, blood pressure was 164/92 mmHg, O₂ saturation was 98% in room air, and body temperature was 36.8 °C. Notable examination finding included slight pretibial pitting edema. Musculoskeletal and neurological examination was unremarkable. There was no conjunctival pallor, hepatosplenomegaly, tenderness in the lumbosacral area, or urticarial skin lesion. There was no sign of diabetic retinopathy or dilatation of the retinal vein in the funduscopy. One year prior to this presentation, his renal function was as follows:

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blood urea nitrogen (BUN) 14.1 mg/dL; sCr 0.97 mg/dL; and estimated glomerular filtration rate (eGFR) 60 mL/min per 1.73 m². On his current admission, laboratory findings included a normal red blood cell level ($5.2 \times 10^{12}/L$), a normal white blood cell level ($7.8 \times 10^9/L$), and a normal platelet count ($31.0 \times 10^9/L$). Additionally, the bilirubin level was 0.5 mg/dL (normal: 0.3–1.2 mg/dL), the alanine transaminase 20 U/L (normal: 5–45 U/L), the aspartate aminotransferase level was 22 U/L (normal: 5–45 U/L), the alkaline phosphatase 295 U/L (normal: 104–398 U/L), and the lactate dehydrogenase level was 101 U/L (normal: 120–145 U/L). A severely worsening of kidney function (BUN 14.0 mg/dL; sCr 4.13 mg/dL; eGFR 12 mL/min per 1.73 m²) was noted using the Hitachi type-7 Auto analyzer[®] and the enzymatic method by Pure-auto S CRE-N[®]. Additionally, the total protein was 8.2 g/dL, albumin level was 4.6 g/dL, glucose level was 168 mg/dL, and hemoglobin A1c level was 8.0% (National Glycohemoglobin Standardization Program). The direct Coombs test was negative. The immunoglobulin levels were normal (IgG 676 mg/dL; IgA 145 mg/dL), except for elevated IgM (1856 mg/dL). Antinuclear antibodies, anti-mitochondrial antibody, antineutrophil cytoplasm antibodies, and glomerular basement membrane antibody were negative; also, complement levels were normal (C3 64 mg/dL; C4 20 mg/dL; CH50 39 IU/mL). Cryoglobulin was negative. Urinalysis showed mild proteinuria (0.18 g/day) without microhematuria (< 1 erythrocyte per high-power field) and no cast was noted. The size of the kidneys was normal on renal sonography. A repeat creatinine measurement 1 week later using the same technology showed his BUN as 14.5 mg/dL and sCr as 5.31 mg/dL. Hypoglycemic medication was changed from metformin to linagliptin. Renal biopsy showed ten glomeruli; all of them had minor glomerular abnormalities and none of them had infiltration of mononuclear leukocytes or duplication of the glomerular basement membranes. There was no nodular glomerulopathy or tubular cast formation. Immunofluorescence microscopy showed no deposition of κ chain and λ chain. There was no amyloid deposit on Congo red staining. Electron microscopy could not be performed because of insufficient specimens. The results of the renal biopsy could not identify the etiology of the elevating sCr. However, we found an elevated total protein (8.2 g/dL) and lowering of the BUN and sCr ratio from 14.5 to 2.7. Plasma cell disorders, including multiple myeloma, Waldenström macroglobulinemia, and monoclonal gammopathy of undetermined significance, were considered. An elevated level of serum IgM (1856 mg/dL) and the presence of Bence Jones protein in urine protein electrophoresis also supported this suspicion. We performed serum protein electrophoresis, which revealed a monoclonal IgM κ . Free light-chain ratio was 17.7 (κ chain 220 mg/L; λ chain 12.5 mg/L). A bone marrow biopsy showed $2.57 \times 10^4/\mu L$ of nucleated cell counts and

$4.5/\mu L$ of megakaryocytes. Immunofluorescence microscopy of the bone marrow showed no light-chain restriction pattern of κ chain and λ chain. They were compatible with monoclonal gammopathy of undetermined significance (IgM- κ MGUS). We suspected the elevation of sCr which was caused by IgM- κ MGUS, because the patient's clinical manifestations and renal biopsy were discordant with the degree of abrupt sCr elevation. Therefore, different parameters of the kidney function were investigated. The cystatin C level was 1.05 mg/dL (reference range 0.63–0.95 mg/dL) and the 24-h creatinine clearance was 58 mL/min, suggesting the creatinine measurements using the pure-auto S CRE-N[®] method were inaccurate. Consultation with the clinical laboratory proved the enzymatic creatinine measurement approach had been changed from the pure-auto S CRE-N[®] method to the Shikarikid-S CRE[®] method. We measured the sCr using the Shikarikid-S CRE[®] method, which revealed a creatinine level of 0.97 mg/dL, corresponding to the previous sCr level. The final diagnosis of a falsely elevated sCr level caused by IgM- κ MGUS was made. In cooperation with the clinical laboratory, we confirmed that patient's sCr concentration was within the reference range using the patient's serum sample in different dilution ratio, which is defined as the patient serum sample divided by the 0.9% normal saline, from 1/1 to 1/16, and testing with the pure-auto S CRE-N[®] and the pure-auto S CRE-L[®] (Table 1). According to SEKISUI MEDICAL Co., Ltd., [5, 6] a manufacturer of these enzymatic creatinine measurement methods, both of them have high reproducibility and higher sensitivity than other enzymatic methods. Although they may underestimate the measurement of sCr under high concentration of immunoglobulin, they are not interfered by other substance such as bilirubin, ascorbic acid, and hemoglobin. The difference in enzyme element is the major distinction between the two methods: the Pure-auto S CRE-N[®] contains creatinase, sarcosine oxidase, *N*-ethyl-sulfobutyl-*m*-toluidine sodium, catalase, 4-aminoantipyrine, and peroxidase, whereas, the Pure-auto S CRE-L[®] contains creatine amidinohydase, sarcosine oxidase, catalase, *N*-ethyl-*N*-3-sulfopropyl-3-methylaniline, 4-aminoantipyrine, peroxidase, and sodium azide.

We informed the patient of our final diagnosis and the patient accepted our apology for unnecessary tests and procedures. We obtained informed consent for this publication from the patient. One year after commencing linagliptin, HbA1c level decreased from 8.0 to 7.2% and sCr level decreased from 4.31 to 3.42 mg/dL using the Hitachi type-7 Auto analyzer[®] and the enzymatic method by Pure-auto S CRE-N[®]. The cystatin C level remained stable (1.05 mg/dL). The serum IgM level also decreased from 1856 to 1650 mg/dL. He visits our outpatient clinic every 2 months, and has no clinical and laboratory findings that are suggestive of progression to multiple myeloma or related malignant disease to date.

Table 1 Serum creatinine concentration with different dilution ratios and different reagents

Dilution ratio (patient serum/0.9% normal saline)	Reagent #1	Reagent #2	sCr concentration (mg/dL)
1/1	Pure-auto S CRE-L [®]	Pure-auto S CRE-N [®]	7.80
1/2	Pure-auto S CRE-L [®]	Pure-auto S CRE-N [®]	4.80
1/4	Pure-auto S CRE-L [®]	Pure-auto S CRE-N [®]	2.50
1/8	Pure-auto S CRE-L [®]	Pure-auto S CRE-N [®]	1.20
1/16	Pure-auto S CRE-L [®]	Pure-auto S CRE-N [®]	0.40
1/1	Pure-auto S CRE-N [®]	Pure-auto S CRE-L [®]	0.88
1/2	Pure-auto S CRE-N [®]	Pure-auto S CRE-L [®]	0.37
1/4	Pure-auto S CRE-N [®]	Pure-auto S CRE-L [®]	0.11
1/8	Pure-auto S CRE-N [®]	Pure-auto S CRE-L [®]	Under measurement sensitivity
1/16	Pure-auto S CRE-N [®]	Pure-auto S CRE-L [®]	Under measurement sensitivity
1/1	Pure-auto S CRE-N [®]	Pure-auto S CRE-N [®]	1.02
		+ 0.9% normal saline	
1/2	Pure-auto S CRE-N [®]	Pure-auto S CRE-N [®]	0.50
		+ 0.9% normal saline	
1/4	Pure-auto S CRE-N [®]	Pure-auto S CRE-N [®]	0.24
		+ 0.9% normal saline	
1/8	Pure-auto S CRE-N [®]	Pure-auto S CRE-N [®]	0.10
		+ 0.9% normal saline	
1/16	Pure-auto S CRE-N [®]	Pure-auto S CRE-N [®]	0.00
		+ 0.9% normal saline	

sCr serum creatinine

Discussion

In the present case, we made two important clinical observations. First, MGUS can present with false serum creatinine elevation. MGUS is a premalignant clonal plasma cell or lymphoplasmacytic proliferative disorder, defined by the presence of a serum monoclonal protein (M protein) concentration lower than 3 g/dL, a bone marrow with less than 10% monoclonal lymphoplasmacytic infiltration, and absence of end-organ damage (lytic bone lesions, anemia, hypercalcemia, and renal insufficiency) related to the M protein [1–3]. It is usually detected as an incidental laboratory finding [4], and patients with MGUS, by definition, have no signs and symptoms of multiple myeloma or related malignancy that can be attributed to their monoclonal protein. However, circulating monoclonal proteins can interfere with laboratory tests, and several articles have reported their laboratory artifacts, including HDL cholesterol, bilirubin, inorganic phosphate, bicarbonate, and iron [7–16]. In contrast, case reports of renal abnormality associated with MGUS are rare, and only four cases have been reported. These reports are summarized in Table 2: case 1 involved a 63-year-old man, case 2 involved an 80-year-old man, case 3 involved a 72-year-old man, and case 4 (the age and gender are unknown) [17–20]. To our knowledge, this patient had the longest follow-up period among those with a falsely elevated sCr due to

MGUS. Although the exact mechanisms through which M protein interferes with the measurement of sCr remain controversial, one potential mechanism is precipitation of M protein, resulting in increased turbidity of the sample [8, 19, 21, 22]. Another mechanism is that M protein forms a complex with reagents and interferes with measurement of the enzymatic reaction [17, 23]; however, this has only been observed in the context of the Jaffé method [24]. A less frequent mechanism is caused by a higher viscosity due to a very high M protein concentration or gel formation in a refrigerated sample, as is the case in cryoglobulinemia [23]. In our case, we confirmed the paraprotein interfered with only Pure-auto S CRE-N[®].

Our second observation is that the measurement of cystatin C is useful for the diagnosis of this condition. Cystatin C, a 122-amino acid protein with a molecular mass of 13-kDa, is one of the accurate biomarkers of glomerular filtration, because it is freely filtered at the renal glomeruli and approximately 99% of the filtered cystatin C is reabsorbed by the proximal tubular cells [25, 26]. Cystatin C has several advantages over sCr, which includes: cystatin C is not affected by age, sex, race, and muscle mass [25, 26], and cystatin C has a lower interindividual variability than sCr [27].

This case report has several limitations. First, we did not measure sCr with other specific methods such as isotope

Table 2 Case summary of pseudohypercreatinemia due to MGUS

Case no. Age/gender	IgM (g/l)	Enzymatic sCr (md/dL)	Jaffe sCr (mg/dL)	HPLC sCr (mg/dL)	Cystatin C (mg/dL)	24 h-CCr (mL/min)
Case 1 [15] 63/male	28.6	2.7	1.2			
Case 2 [16] 80/male	6.5	4.3		1.1		
Case 3 [17] 72/male	3.6	4.5				
		1.2 (another kit)				
Case 4 [18] Unknown/unknown	Unknown	3.3	2.0	1.0		
Our case	18.6	4.13 (Pure-auto S CRE-N®) 0.92 (Shikarikiid-S CRE-N®)			1.05	58

sCr serum creatinine, HPLC hyperliquid chromatography, CCr creatinine clearance

dilution mass spectroscopy and liquid chromatography; however, neither of them is routinely performed in daily clinical practice [17, 19]. Second, cystatin C has the issue of immunoassay standardization. Automated latex particle-enhanced turbidimetric immunoassay from Dako or particle-enhanced nephelometric immunoassay from Dade Behring has been used; however, each has its weaknesses [28, 29]. However, we utilized a sol particle immunoassay for measuring serum cystatin C, which is sensitive, precise, stable, and compatible with various commercial analyzers [30]. Third, this case might be smoldering Waldenström macroglobulinemia, because serum κ chain disproportionally increased compared to serum λ chain. However, this was less likely because this case did not fulfill the criteria of smoldering Waldenström macroglobulinemia. Fourth, the patient has only been followed up for 1 year, even though our patient has a longer follow-up period than other reported cases [17–20]. Long-term follow-up is important, because IgM MGUS may progress to lymphoplasmacytic lymphoma or other B-cell lymphomas [3, 31].

Conclusion

In summary, we report a case of MGUS, presenting with elevated sCr, and had M protein interference with a laboratory assay. The patient was confirmed to have a false sCr elevation due to increased turbidity by precipitation of M protein. This condition can be recognized in patients with a normal BUN or elevated total protein; thus, measuring the renal function using cystatin C is important in patients with paraproteinemia and should be considered in patients with suspected monoclonal immunoglobulin-associated renal disease to avoid unnecessary tests or procedures.

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Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted (IRB approval number: 2017-125) and followed the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

- Kyle RA. Monoclonal gammopathy of undetermined significance: natural history in 241 cases. *Am J Med.* 1987;64:814–26.
- Kyle RA, Therneau TM, Rajkumar SV, Larson DR, Plevak MF, Melton LJ III. Long-term follow-up of 241 patients with monoclonal gammopathy of undetermined significance: the original Mayo Clinic series 25 years later. *Mayo Clin Proc.* 2004;79:859–66.
- Kyle RA, Larson DR, Therneau TM, Despenzieri A, Kumar S, Cerhan JR. Long-term follow-up of monoclonal gammopathy of undetermined significance. *N Engl J Med.* 2018;378:241–9.
- Rajkumar SV. Plasma cell disorders. In: Goldman L, Schafer AI, editors. *Goldman-Cecil Medicine*. 25th ed. Philadelphia: Elsevier Saunders; 2016. p. 1273–1284.
- Berth M, Delanghe J. Protein precipitation as a possible important pitfall in the clinical chemistry analysis of blood samples containing monoclonal immunoglobulins: 2 case reports and a review of the literature. *Acta Clin Belg.* 2004;59:263–73.
- Pure-auto S CRE-N®. SEKISUI MEDICAL Co., Ltd. 2017. https://www.info.pmda.go.jp/tgo/pack/20800AMZ10178000_A_01_07/ Accessed 05 Nov 2019. (in Japanese)
- Pure-auto S CRE-L®. SEKISUI MEDICAL Co., Ltd. 2017. https://www.info.pmda.go.jp/tgo/pack/21300AMZ00422000_A_01_05/ Accessed 05 Nov 2019. (in Japanese)
- Smogorzewska A, Flood JG, Long WH, Dighe AS. Paraprotein interference in automated chemistry analyzers. *Clin Chem.* 2004;50:1691–3.
- Tsai LY, Tsai SM, Lee SC, Liu SF. Falsely low LDL-cholesterol concentrations and artifactual undetectable HDL-cholesterol

- measured by direct methods in a patient with monoclonal paraprotein. *Clin Chem Acta*. 2005;358:192–5.
10. Pantanowitz L, Horowitz GL, Upalakalin JN, Beckwith BA. Artifactual hyperbilirubinemia due to paraprotein interference. *Arch Pathol Lab*. 2003;127:55–9.
 11. Murali MR, Kratz A, Finberg KE. Case records of the Massachusetts General Hospital. Case 40–2006. A 64-year-old man with anemia and a low level of HDL cholesterol. *N Engl J Med*. 2006;355:2772–9.
 12. Alyanakian MA, Taes Y, Bensaïd M, Segovia B, Aucouturier P, Rain JD, et al. Monoclonal immunoglobulin with antitransferrin activity: a rare cause of hypersideremia with increased transferrin saturation. *Blood*. 2007;109:359–61.
 13. Krish P, Jhaveri KD. Hyperbicarbonatemia in a patient with Waldenström's macroglobulinemia Pseudohyperbicarbonatemia due to paraproteinemia. *Kidney Int*. 2012;81:603–5.
 14. Yang Y, Howanitz PJ, Howanitz JH, Gorfajn H, Wong K. Paraproteins are a common cause of interferences with automated chemistry methods. *Arch Pathol Lab Med*. 2008;132:217–23.
 15. Miyoshi M, Nishioka M, Hata M, Nakao T, Doi T. Comparative study of measurement error for creatinine concentration in serum six reagents. *Jpn J Med Tech*. 2017;66:547–53 (in Japanese).
 16. Yamaki M. A case of pseudohypercreatinemia in a patient suffering from macroglobulinemia. *Jpn J Nephrol*. 2004;46:43–8 (in Japanese).
 17. Storsley L, Fine A, Krahn J. IgM monoclonal protein presenting as pseudohypercreatinemia. *Nephrol Dial Transplant*. 2006;21:3337–8.
 18. Ikeda M, Tsukamoto T, Miyake T, Kakita H, Komiya T, Yone-moto S, et al. A case of pseudohypercreatinemia associated with monoclonal IgM gammopathy. *Jpn J Nephrol*. 2013;55:1340–4 (in Japanese).
 19. Kadatz MJ, Lee ES, Duncan J, Levin A, Johnson O. A peculiar case of Paraproteinemia and elevated creatinine. *Am J Kidney Dis*. 2018;71:xiv–xv.
 20. Hummel KM, von Ahsen N, Kühn RB, Grunewald RW, Oellerich M, Müller GA. Pseudohypercreatinemia due to positive interference in enzymatic creatinine measurements caused by monoclonal IgM in patients with Waldenström's macroglobulinemia. *Nephron*. 2000;86:188–9.
 21. Rudofsky G, Villalobos M, Waldherr R, Schair M, Zorn M, Maimer A, et al. Renal failure in a male with Waldenström's macroglobulinemia. *Kidney Int*. 2010;77:371–2.
 22. Kwok J, Chow KM, Lit L, Chan M. Paraproteinemia-associated pseudohypercreatinemia across different analytical methodologies. *Kidney Int*. 2010;78:621.
 23. Sheppard CR, Allen RC, Austin GE, Young AN, Ribeiro MA, Fantz CR. Paraprotein interference in automated chemistry analyzers. *Clin Chem*. 2005;51:1077–8.
 24. Reed RG. Interference by an IgM paraprotein in the bromocresol green method for determination of serum albumin. *Clin Chem*. 1987;33:1075–6.
 25. Coll E, Botey A, Alvarez L, Poch E, Quinto L, Saurina A, et al. Serum cystatin C as a new marker for noninvasive estimation of glomerular filtration rate and as a marker for early renal impairment. *Am J Kidney Dis*. 2000;36:29–34.
 26. Ferguson MA, Waiker SS. Established and emerging markers of kidney function. *Clin Chem*. 2012;58:680–9.
 27. Keevil BG, Kilpatrick ES, Nichols SP, Maylor PW. Biological variation of cystatin C: implications for the assessment of glomerular filtration rate. *Clin Chem*. 1998;44:1535–9.
 28. Kyhse-Andersen J, Schmidt C, Nordin G, Andersson B, Nilsson-Ehle P, Lindstöm V, et al. Serum cystatin C, determined by a rapid, automated particle-enhanced turbidimetric method, is a better marker than serum creatinine for glomerular filtration rate. *Clin Chem*. 1994;40:1921–6.
 29. Mussap M, Ruzzante N, Varagnolo M, Plebani M. Quantitative automated particle-enhanced immunonephelometric assay for the routine measurement of human cystatin C. *Clin Chem Lab Med*. 1998;36:859–65.
 30. Tanaka M, Matsuo K, Enomoto M, Mizuno K. A sol particle homogenous immunoassay for measuring serum cystatin C. *Clin Biochem*. 2004;37:27–35.
 31. Tanaka H, Sakuma Y, Ikeda H, Shimizu R, Sugita Y, Iwai R. Characteristics and prognosis of patients with immunoglobulin M monoclonal gammopathy. *J Clin Exp Hematop*. 2017;57:47–53.

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