AJKD
Acid-base and Electrolyte Teaching Case

A 90-Year-Old Man With Hyperphosphatemia

Shachi Lovekar, MD, and Joline L.T. Chen, MD, MS

Hyperphosphatemia is a common condition in patients with decreased kidney function, and without treatment, it can lead to a variety of clinical consequences. However, the presence of hyperphosphatemia in patients with normal kidney function may be true or spurious. We present a case of pseudohyperphosphatemia in a patient with monoclonal gammopathy. An increased paraprotein level can lead to colorimetric interference of the assay of phosphate measurement and result in spurious hyperphosphatemia. The epidemiologic and clinical characteristics of paraprotein-associated pseudohyperphosphatemia also are reviewed here. Ultrafiltration of paraproteins or deproteinization can help correct the measuring error. Patients with spurious hyperphosphatemia should not be treated with phosphate binders. Clinicians treating patients with monoclonal gammopathy should be aware of this relatively common clinical phenomenon and avoid inappropriate treatment of spurious hyperphosphatemia.
Am J Kidney Dis. 57(2):342-346.

INDEX WORDS: Spurious; hyperphosphatemia; pseudohyperphosphatemia; monoclonal gammopathy; paraprotein; molybdate.

INTRODUCTION

Hyperphosphatemia is defined as an increase in circulating phosphorus levels to greater than the reference range of 2.5-4.5 mg/dL (0.81-1.45 mmol/L) for an adult. Circulating phosphorus complexes with calcium and can cause severe and potentially symptomatic hypocalcemia, tissue deposition of calcium-phosphate complexes, secondary hyperparathyroidism in patients with chronic kidney disease, and worsening kidney function from phosphate nephropathy.

CASE REPORT

Clinical History and Initial Laboratory Data

A 90-year-old man was referred for evaluation of nephrotic-range proteinuria in December 2008. Proteinuria initially was noted in May 2008 with a 24-hour urine collection, with protein excretion of 2.0 g/d. Incidentally, he was noted to have an increased phosphorus level of 5.0 mg/dL (1.61 mmol/L) and serum creatinine level of 1.1 mg/dL (97.24 μmol/L). The measured creatinine was traceable to isotope-dilution mass spectrometry, and estimated glomerular filtration rate, calculated using the 4-variable MDRD (Modification of Diet in Renal Disease) Study equation, was 63 mL/min/1.73 m^2 (1.05 mL/s/1.73 m^2). He did not have symptoms or signs of hyperphosphatemia or hypocalcemia. He did not report using dietary protein supplements, having excessive dairy product intake, or using phosphate soda preparation in the recent past. He had never undergone parathyroid or thyroid surgery.

The patient's medical history was significant for hypertension, anemia, chronic back pain, osteoporosis, and immunoglobulin G (IgG) κ monoclonal gammopathy of undetermined significance (MGUS). MGUS was diagnosed in May 2006 during a workup for back pain and anemia. A bone marrow biopsy then had shown 10%-15% primarily mature plasma cells expressing monoclonal κ light chains on their surface. During the following 3 years, he was believed to be clinically stable without evidence of progression to myeloma.

The patient's social history revealed 80 pack-year cigarette smoking. He reported angioedema from angiotensin-converting enzyme inhibitors. His medications included risedronate, furosemide, and amlodipine. Review of systems was positive for joint pains and recent onset of leg swelling. Physical examination was significant for blood pressure of 168/77 mm Hg and moderate peripheral edema, but otherwise was unremarkable.

Other significant laboratory studies at this visit included albumin level of 3.0 g/dL (30 g/L), calcium level of 8.3 mg/dL (2.07 mmol/L), and spot urine protein-creatinine ratio of 5.9 g/g, as listed in Table 1. A subsequent kidney biopsy showed extensive podocyte effacement, early nodular glomerulosclerosis without direct damage from paraproteinemia, and no evidence of myeloma kidney. Laboratory studies at a follow-up visit about 7 months later were notable for spontaneous improvement in proteinuria, with a spot urine protein-creatinine ratio of 1.0 g/g. Meanwhile, phosphorus level had increased to 9.9 mg/dL (3.20 mmol/L), whereas creatinine level was 1.3 mg/dL (114.92 μmol/L) and estimated glomerular filtration rate was 51 mL/min/1.73 m^2 (0.85 mL/s/1.73 m^2). The patient remained without symptoms or signs of hyperphosphatemia.

Additional Investigations

Investigations for the hyperphosphatemia included workup for rhabdomyolysis, hypoparathyroidism, and hemolysis, but the patient did not have symptoms or clinical evidence of these diseases. He also was instructed to discontinue risedronate therapy and decrease dietary protein intake. A repeated serum phosphorus level was 9.1 mg/dL (2.94 mmol/L).

Because of concern about pseudohyperphosphatemia, phosphorus was retested by dividing the patient's blood sample into 2 portions. For the initial test, 2-5 mL of serum was centrifuged

From the Renal Section, Department of Medicine, Boston University School of Medicine, Boston, MA.

Received March 26, 2010. Accepted in revised form July 9, 2010. Originally published online October 18, 2010.

Address correspondence to Joline L.T. Chen, MD, MS, Renal Section, Department of Medicine, EBRC Bldg, Ste 504, 650 Albany St, Boston, MA 02118. E-mail: joline.chen@bmc.org

0272-6386/$36.00
doi:10.1053/j.ajkd.2010.07.017

Table 1. Clinical Laboratory Data

Parameter	5/29/08[a]	12/10/08	2/11/09	7/8/09	Reference Range
Serum studies					
Hemoglobin (g/dL)	11.6	10.0	11.0	10.2	13.5-18
Serum creatinine (mg/dL)	1.03	1.14	1.40	1.31	0.8-1.3
eGFR[b] (mL/min/1.73 m^2)	68	60	48	51	
Calcium (mg/dL)	8.9	8.3	8.4	9.0	8.4-10.2
Phosphorus (mg/dL)		5.0	6.2	9.9	2.5-4.5
25 Hydroxyvitamin D_3 (ng/mL)				22.4	30-60[c]
1,25 Dihydroxyvitamin D (pg/mL)				36	25-66
Parathyroid hormone (pg/mL)				25	11-80
Albumin (g/dL)		3.0	3.3	3.6	3.5-4.8
Free calcium (mg/dL)				4.5	3.8-5.3
Uric acid (mg/dL)				7.2	3.4-7.0
Creatine kinase (U/L)				79	39-259
Thyrotropin (μIU/mL)				2.44	0.35-5.5
Urinary studies					
24-h urine protein (mg)	2,043				
24-h urine creatinine (mg)	580				
Spot urine protein (mg/L)	3,000	2,188	1,201	574	
Spot urine creatinine (mg/L)	1,000	372	570	569	
Serum immunofixation electrophoresis					
IgA (mg/dL)	79			53	70-400
IgG (mg/dL)	2,580			4,060	700-1,600
IgM (mg/dL)	41			22	46-304
κ (mg/dL)	1,880			5,220	574-1,276
λ (mg/dL)	183			166	269-638
κ:λ ratio	15.7			31.4	1.0-2.5
Free light chain analysis					
λ (mg/L)	72	67.6		56.1	5.7-26.3
κ (mg/L)	71.3	83.7		147.0	3.3-19.4
κ:λ ratio	0.99	1.24		2.62	0.26-1.65

Note: Conversion factors for units: hemoglobin from g/dL to g/L, ×10; serum creatinine in mg/dL to μmol/L, ×88.4; serum calcium from mg/dL to mmol/L, ×0.2495; serum phosphorus from mg/dL to mmol/L, ×0.3229; 25 hydroxyvitamin D from ng/mL to nmol/L, ×2.496; 1,25 dihydroxyvitamin D from pg/mL to pmol/L, ×2.6; albumin from g/dL to g/L, ×10; serum uric acid from mg/dL to μmol/L, ×59.48; IgA from mg/dL to mg/L, ×10; IgG from mg/dL to g/L, ×0.01; IgM from mg/dL to mg/L, ×10; eGFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, ×0.01667. No conversion necessary for serum parathyroid hormone from pg/mL to ng/L.

Abbreviations: eGFR, estimated glomerular filtration rate; IgA, immunoglobulin A.

[a]Six months before the first nephrology visit.

[b]eGFR was calculated using the 4-variable MDRD (Modification of Diet in Renal Disease) Study equation.

[c]Ideal range.

for 6-8 minutes and assayed using the Bayer ADVIA 2400 clinical analyzer (Siemens AG, www.medical.siemens.com). The second part of the patient's blood was filtered using an Amicon Ultra 30000 filter (Millipore, www.millipore.com), which would remove protein with molecular weight >30 kDa. The filtered blood then was centrifuged for 6-8 minutes and tested on the same analyzer. Results of the initial and repeated phosphorus tests are listed in Table 2.

As listed in Table 1, the repeated IgG level showed a significant increase to 4,060 mg/dL (40.60 g/L) from a level of 2,580 mg/dL (25.80 g/L) 1 year prior. In addition, serum κ to λ free light chain ratio was increased to 2.62 compared with 1.24 one year ago.

Diagnosis

Pseudohyperphosphatemia; MGUS, possibly progressing to multiple myeloma.

Table 2. Phosphorus Levels With and Without Filtration

Parameter	7/8/09	7/10/09	7/31/09	11/16/09
Serum creatinine (mg/dL)	1.31		1.15	1.65
eGFR[a] (mL/min/1.73 m^2)	51		60	39
Prefiltration phosphorus (mg/dL)	9.9	9.1	6.2	12.9
Postfiltration phosphorus (mg/dL)		4.4	3.9	4.8

Note: The filter used had a 30-kDa molecular weight cutoff. Conversion factors for units: serum creatinine in mg/dL to μmol/L, ×88.4; serum phosphorus from mg/dL to mmol/L, ×0.3229; eGFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, ×0.01667.

Abbreviation: eGFR, estimated glomerular filtration rate.

[a]eGFR was calculated using the 4-variable MDRD (Modification of Diet in Renal Disease) Study equation.

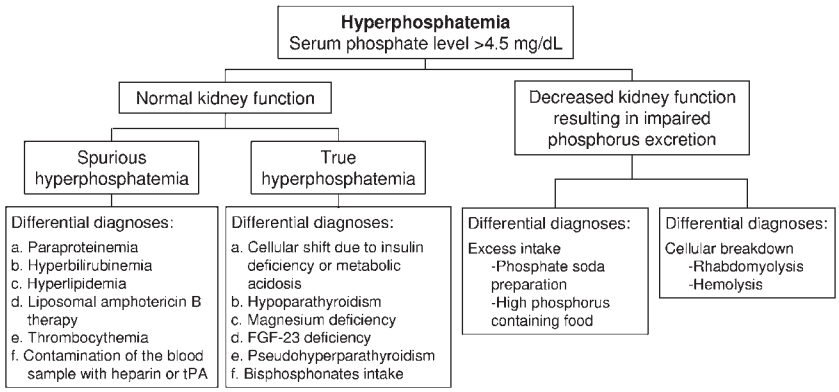

Figure 1. Algorithm to approach hyperphosphatemia. Abbreviations: FGF-23, fibroblast growth factor 23; tPA, tissue plasminogen activator.

Clinical Follow-up

A hematology re-evaluation was planned for suspected progression of MGUS to multiple myeloma. However, in the interim, the patient experienced an ischemic stroke and a joint decision was made not to pursue further aggressive measures in his care.

DISCUSSION

Multiple myeloma can cause true hyperphosphatemia in the setting of tumor lysis or decreased kidney function. However, clues that hyperphosphatemia is spurious may be present when a patient has relatively normal kidney function, no clinical features of hyperphosphatemia, and normal calcium levels.[1]

Pseudohyperphosphatemia in the setting of multiple myeloma primarily has been reported after the introduction of the colorimetric assay to measure inorganic phosphorus in clinical laboratories. Our patient's initial sample was tested using a clinical analyzer in which inorganic phosphorus reacts with ammonium molybdate in the presence of sulfuric acid to form an unreduced phosphomolybdate complex. This phosphomolybdate complex absorbs light and is quantified photometrically in the UV range at a wavelength of 340 nm. Light absorbance is directly proportional to the inorganic phosphorus concentration.

Two mechanisms have been hypothesized to explain pseudohyperphosphatemia. First, paraproteins bind to molybdate, resulting in turbidity. The turbid reaction mixture scatters and absorbs light while reducing its transmittance. This then can be interpreted as a falsely high phosphorus level. The second proposed mechanism for spurious hyperphosphatemia is the direct binding of paraprotein to phosphorus.[2,3] Mandry et al[2] have shown in vitro the binding of inorganic phosphate to IgG-coated beads in patients with or without multiple myeloma. However, the same finding was not shown consistently in other studies.[4] For example, Barutcuoglu et al[4] questioned whether deproteinization would lead to precipitation of phosphorus loosely bound to plasma protein. They compared inorganic phosphate values in serum samples from control participants without paraproteinemia before and after deproteinization with sulfosalicylic acid and found no difference in phosphate values. The conclusion was that inorganic phosphate was not directly bound to plasma protein molecules. Another plausible explanation may be that phosphorus binding, if responsible for pseudohyperphosphatemia, would be a property of the paraprotein itself. Further research is required to elucidate these properties.

Measuring phosphate using the direct ammonium molybdate method has been associated with the highest incidence of pseudohyperphosphatemia compared with the modified molybdate method, enzymatic methods,[5,6] atomic spectrophotometry, or methods involving deproteinization of serum samples. Deproteinization can be achieved using dialysis,[7] acid precipitation,[4,7-9] or filtration.[7,10] Although some studies used simple dilution of the sample to eliminate turbidity and interference,[11] in other studies, dilution had limited success[7] or failed in eliminating interference.[4]

A few investigators have performed larger scale studies evaluating sera from 30-298 patients with paraproteinemias to better understand the characteristics of the paraproteins that may lead to interference in the colorimetric assay. A reported 8%-49% of patients with monoclonal gammopathy or myeloma can show pseudohyperphosphatemia.[5-7,12,13] IgG levels of 2,000-64,000 mg/dL have been documented to be associated with pseudohyperphosphatemia.[6] Paraprotein levels correlated positively with turbidity in the direct molybdate method[6] and correlated with phosphorus levels in turbid samples.[1,4,6,14] However, this association has not been shown universally in all studies.[5] Although pseudohyperphosphatemia has been documented mostly in patients with IgG paraproteinemia, it also has been reported in association with IgA paraproteinemia.[15,16] Others have found no relation between the type of paraprotein and incidence of pseudohyperphosphatemia.[5,6,10,13]

In general, treatment is not necessary if the true phosphorus value is within the reference range and the patient is asymptomatic. The possibility of true hypophosphatemia masked by measured phosphorus val-

Box 1. Teaching Points

- Hyperphosphatemia is common, especially in patients with kidney disease
- In patients with normal kidney function, the presence of an increased phosphorus level should raise suspicion for potential spurious hyperphosphatemia
- Spurious hyperphosphatemia has been reported in patients with monoclonal gammopathy or multiple myeloma. This may be secondary to paraprotein interference in the colorimetric assay, leading to inaccurate measurement of phosphorus
- The true phosphorus level can be rechecked after ultrafiltration of the paraprotein in serum or by acid deproteinization
- No phosphate binder therapy should be initiated for pseudohyperphosphatemia

ues falsely in the reference range also is a consideration. Treatment with chemotherapy or plasma exchange that decreases serum globulin levels often leads to a simultaneous decrease in serum phosphorus levels, although the degree of change in phosphorus levels may not correlate with the degree of change in globulin levels.[9,17-19]

Although pseudohyperphosphatemia has been reported mostly in patients with multiple myeloma and Waldenström macroglobulinemia, other causes, such as hyperbilirubinemia,[20] hyperlipidemia,[21] hepatosplenic schistosomiasis,[22] liposomal amphotericin B therapy,[23,24] and contamination with phosphate containing saline,[25] heparin, or tissue plasminogen activator[26,27] also have caused spurious hyperphosphatemia because they can also interfere with the colorimetric assay. Figure 1 shows the differential diagnoses and approaches to patients with increased phosphate levels. Importantly, rare incidences of pseudohypophosphatemia have been reported in association with paraproteinemias, which also can lead to laboratory interference of a paradoxical direction.[28-31]

In conclusion, hyperphosphatemia is not uncommon. Clinicians taking care of patients with monoclonal gammopathy need to be aware of the potential interference in phosphate-measuring assays that can result in spurious phosphate values. A diagnosis of pseudohyperphosphatemia must be suspected when a patients' phosphorus level is increased out of proportion to the degree of kidney disease, with normal calcium, parathyroid hormone, and vitamin D levels (See Box 1 for case teaching points). Further workup is necessary to evaluate the cause of hyperphosphatemia and prevent inappropriate treatment.

ACKNOWLEDGEMENTS

The authors acknowledge the support of the patient and the medical team involved in the care of this patient. Specifically, the authors thank Opoku Adjapong, MD, and Steven Bogen, MD, PhD, for helpful input and medical expertise.

Support: None.

Financial Disclosure: The authors declare that they have no relevant financial interests.

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