Clinical Research Clinical Medicine Pathology

Pseudohyperphosphatemia in multiple myeloma: A commonly misdiagnosed phenomenon

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Abstract

Hyperphosphatemia is a serious condition more commonly seen in renal failure or parathyroid dysfunction. Severe hyperphosphatemia may result in neurological dysfunction, seizure or sudden death from cardiac arrest from widespread tissue calcium deposition. On the other hand, pseudohyperphosphatemia is a phenomenon wherein the laboratory estimation of phosphate is falsely elevated due to interference by other abnormal constituents of serum more commonly in paraproteinemias. Such laboratory errors could trigger multiple laboratory and radiological investigations thus raising the healthcare expenditure. We demonstrate one such case of spurious phosphate elevation where inappropriate treatment with phosphate lowering drugs could have resulted in serious consequences. Moreover, knowledge of this phenomenon may actually be helpful in predicting the presence of smoldering multiple myeloma in patients with monoclonal gammopathy.

Keywords oncology, pathology, multiple myeloma, clinical medicine

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Received Sep 29 2014 Accepted Dec 2 2014 Published Dec 17 2014

Citation Vaidya GN, Bhattad VB, Aggarwal A (2014) Pseudohyperphosphatemia in multiple myeloma: a commonly misdiagnosed phenomenon. *Science Postprint* **1**(1): e00039. doi:10.14340/spp.2014.12C0002.

Funding This case report was not supported by any funds to be disclosed.

Competing interest We hereby declare that we have no conflicts of interest.

Ethics Statement The manuscript was designed ensuring quality and integrity of the research. An informed consent was obtained from the patient voluntarily and all measures were taken to respect the confidentiality and anonymity of the patient. This case report was prepared in accordance with the principals in the Declaration of Helsinki and approval of the ethics committee was obtained.

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Introduction

Pseudohyperphosphatemia is a phenomenon not widely known in clinical practice and can result in serious errors in judgment from clinicians. It may not only result in inappropriate treatment of a non-existent condition but may also mask an underlying true hypophosphatemia [1, 2] .

This spuriously elevated phosphate level tends to increase with increase in the abnormal monoclonal proteins and hence it could be used as a marker of smoldering multiple myeloma [1] or the tumor burden [3] .

Patients and methods

Sixty-eight-year-old African American male was consulted to the nephrology clinic for elevated creatinine and microalbuminuria. The patient was asymptomatic and the lab results were detected during routine PCP follow up visits. He had a past medical history of hypertension, congestive heart failure, diabetes mellitus and papillary thyroid carcinoma status post total thyroidectomy. His relevant home medications included carvedilol, furosemide, amlodipine, gemfibrozil and rosuvastatin.

Clinical findings

Initial laboratory investigations revealed a creatinine level of 2 mg/dL, increased from a baseline of 1.3 mg/dL showing a progressive trend upwards. The rest of the relevant lab results included hemoglobin 11.6 g/dL, hematocrit 35.2%, total protein 7.2 g/dL, albumin 3.6 g/dL. Previous records revealed that the patient had occasional elevations in the past, which coincided with contrast administration for procedures like cardiac catheterization. Also noted was an elevated spot urine protein of 1.6 g/L. Serum protein electrophoresis, done as a part of the proteinuria workup, revealed a monoclonal spike of 0.49 g/dL of IgG lambda confirmed in 6 months but no measurable urinary light chains could be found. He was referred to the hematology/oncology clinic for evaluation of the small monoclonal spike in serum.

Subsequently, he was initially diagnosed as monoclonal gammopathy of unknown significance as the spike was less than 1.5 g/dL refuting the need for multiple myeloma workup. He was followed up every 6 months with serum immunofixation for IgG lambda which showed a trend upwards over 6 years to 1.61 g/dL on immunofixation. Incidentally in the same time period, patient's phosphate similarly showed a trend upwards despite stable calcium levels and renal function, reaching a peak level of 5.2 mg/dL (Figure 1). Patient was asymptomatic during the entire period with stable renal function and normal calcium levels (Figure 2, 3), and the cause of this spurious elevation was not clear upfront. Moreover, further workup revealed a high Parathyroid hormone of 95.2 pg/mL (range 8.5–72.5) and a normal vitamin D level of 41ng/mL (range30–100 ng/mL). Review of literature revealed the unusual laboratory error of pseudohyperphosphatemia, associated with paraproteinemias. The hyperphosphatemia was thought to be spurious because the parathyroid hormone level was normal and serum creatinine as well as estimated GFR were not significantly changed. In order to prove the pseudo-elevation of serum phosphate and remove any interference, patient's serum was treated with sulfosalicylic acid to deproteinize the sample and the measured phosphate level in the sample was 3.4 mg/dL while it was 5.2 mg/dL in an untreated sample.

The patient underwent bone marrow biopsy which showed 10% plasma cells. PET scan performed later was negative and he was diagnosed with smoldering multiple myeloma as he continued to remain asymptomatic.

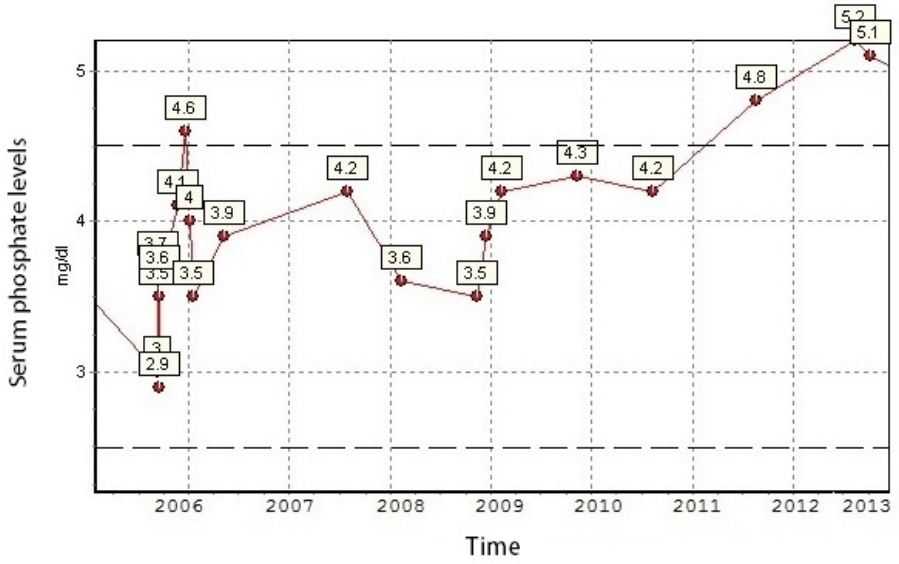

Figure 1 **Phosphate level spuriously peaked in 2013 when he was diagnosed with smoldering multiple myeloma**

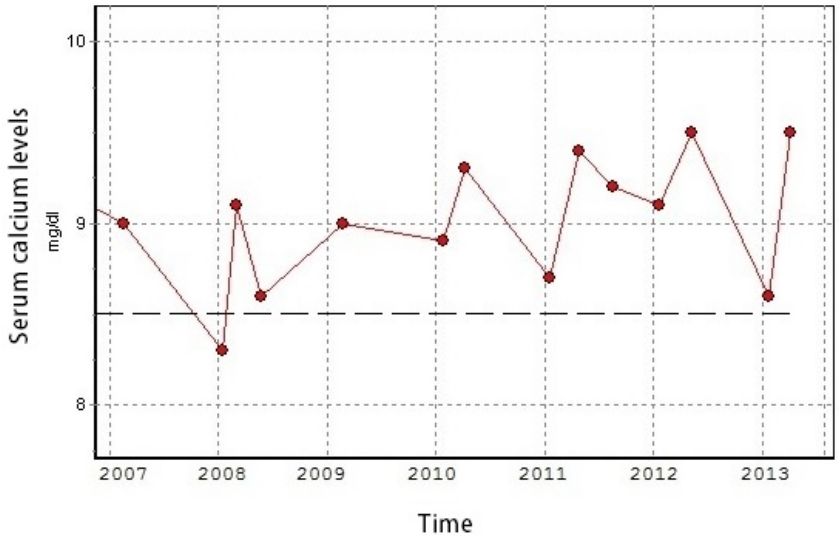

Figure 2 **Showing normal calcium levels during the same time period**

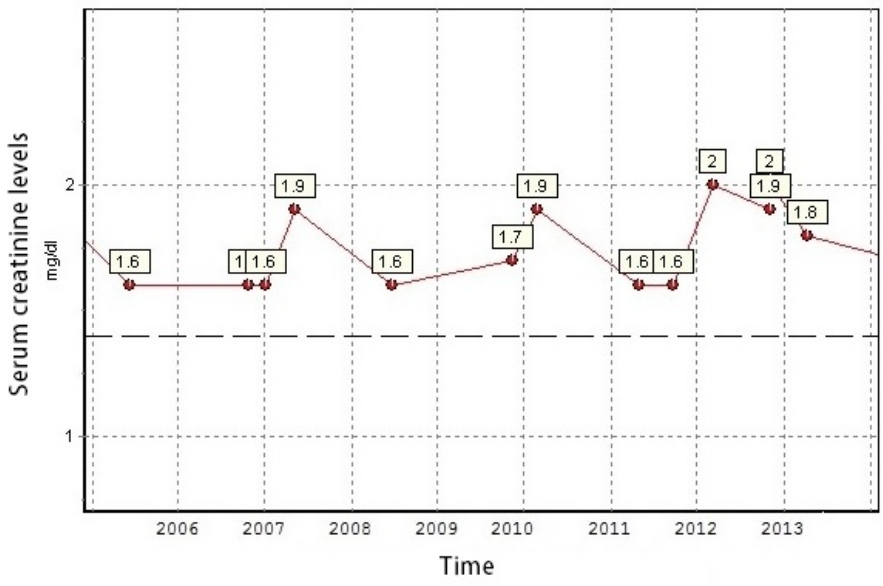

Figure 3 **Showing stable creatinine level**

Discussion

Hyperphosphatemia is a serious condition, indicative of an underlying organ dysfunction or a fatal disease. Hyperphosphatemia occurs in parathyroid disorders, renal failure or may even be a marker of tumor lysis syndrome. Pseudohyperphosphatemia, on the other hand, is a phenomenon wherein the laboratory measurement of phosphate is falsely elevated due to interference by other abnormal constituents of serum especially paraproteins. Such laboratory errors can not only be a cause of concern for the patient and the clinician but also increase the healthcare expenditure by subjecting the patients to numerous laboratory and radiological investigations. It may even mask an underlying true hypophosphatemia [1, 2]. Moreover, inappropriate treatment of such patients with phosphate lowering drugs can have serious consequences [1].

The standard laboratory technique for the detection of phosphate level involves the reaction of inorganic phosphates in the serum with ammonium molybdate in an acidic environment to form phosphomolybdate. This colored substrate is then read colorimetrically to estimate the serum phosphate. The inherent flaw in the design of this tests is the dependence of the test on light penetration into the sample, thus any condition that increases the turbidity of the sample would falsely elevate the reading. In paraproteinemias such as multiple myeloma, the presence of paraproteins could increase the serum turbidity by their sheer presence or through their acid precipitation [2]. The abnormal serum proteins may themselves bind phosphate which may spuriously increase the total serum phosphate, but not the biologically active form of phosphate [3]. Moreover, if such patients are treated with phosphate lowering drugs, the measured phosphate level remains unchanged [4], though the actual phosphate levels may continue to fall. Such findings could trigger fatal clinical errors and mis-diagnoses resulting in aggressive and inappropriate treatments.

Our patient's worsening hyperphosphatemia was incongruent with his stable renal function and normal calcium level [3]. Further literature review revealed the phenomenon of pseudohyperphosphatemia, not widely known in clinical practice. As the IgG in the serum rises, so does the measured phosphate level [2], as demonstrated in our case. Though paraproteinemia is the most common cause of pseudohyperphosphatemia, other causes of laboratory interference include hemolysis, hyperbilirubinemia and hyperlipidemia [4] which may be explained similarly.

One of the ways to circumvent this error is to remove the abnormal serum protein [4, 5]. This could be achieved through deproteinization of the sample with acidic substrates such as trichloroacetic acid or sulfosalicylic acid [2] or by employing dry slide technology used in Ortho Vitros analyzer, which utilizes multiple isotropically porous layers that could filter out the paraproteins, thus removing their interference [2, 6].

Lee et al. suggested that the absorbance of light increases with the increase in serum immunoglobulins which itself may be related to the tumor burden [5]. Thus unexplained hyperphosphatemia could be an indicator of an underlying smoldering multiple

myeloma and should prompt clinicians to investigate further.

Conclusions

1. Widespread clinical understanding of this phenomenon can obviate unnecessary hassle, inappropriate tests and healthcare expenditure [1].
2. On the other hand, inappropriate treatment of falsely elevated phosphate can result in serious consequences.
3. Using deproteinized serum samples could circumvent this lab error.
4. Pseudohyperphosphetemia could be considered as an indicator of insidious paraproteinemia.

Author Contributions

Conceived and designed the work: Vaidya GN

Acquired the data: Vaidya GN, Bhattad VB, Aggarwal A

Analyzed and/or interpreted the data: Vaidya GN, Bhattad VB, Aggarwal A

Drafted the work: Vaidya GN, Bhattad VB, Aggarwal A

Revised and approved the work: Vaidya GN, Bhattad VB, Aggarwal A

References

1. Sinclair D, Smith H, Woodhead P (2004) Spurious hyperphosphataemia caused by an IgA paraprotein: A topic revisited. *Ann. Clin. Biochem.* **41**(2): pp. 119–124. doi:10.1258/000456304322879999.
2. Stratta P, Canavese C, Quaglia M, Lazzarich E, Morellini V, Brustia M et al. (2006) A patient with unexplained hyperphosphataemia. *Nephrol. Dial. Transplant* **21**(9):pp. 2664–2666. doi:10.1093/ndt/gfl306.
3. Lee Y, Koo T, Yi JH, Choi JH, Han SW, Park IK et al. (2007) Pseudohyperphosphatemia in a patient with multiple myeloma. *Electrolyte Blood Press.* **5**(2): pp. 131–135. doi:10.5049/EBP.2007.5.2.131.
4. Barutcuoglu B, Parildar Z, Mutaf I, Habif S, Bayindir O (2003) Spuriously elevated inorganic phosphate level in a multiple myeloma patient. *Clin. Lab. Haematol.* **25**(4): pp. 271–274. doi: 10.1046/j.1365-2257.2003.00524.x.
5. Larner AJ (1995) Pseudohyperphosphatemia. *Clin. Biochem.* **28**(4):pp. 391–393. doi:10.1016/0009-9120(95)00013-Y.
6. Lane JW, Rehak NN, Hortin GL, Zaoutis T, Krause PR, Walsh TJ (2008) Pseudohyperphosphatemia associated with high-dose liposomal amphotericin B therapy. *Clin. Chim. Acta* **387**(1–2): pp. 145–149. doi:10.1016/j.cca.2007.08.008.


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