Case report

Spurious hypophosphatemia associated with monoclonal paraproteinemia

Z. MAO1,2,3 and A.C.M. ONG1,2

From the 1Academic Nephrology Unit, The Henry Wellcome Laboratories for Medical Research, University of Sheffield Medical School, Sheffield, UK, 2Sheffield Kidney Institute, Northern General Hospital, Sheffield Teaching Hospitals Foundation Trust, Herries Road, Sheffield, UK and 3Division of Nephrology, Changzheng Hospital, Second Military Medical University, Shanghai, China

Address correspondence to Professor ACM Ong, Academic Unit of Nephrology, The Henry Wellcome Laboratories for Medical Research, University of Sheffield Medical School, Beech Hill Road, Sheffield S10 2RX, UK. email: a.ong@sheffield.ac.uk

Introduction

Hypophosphatemia is a relatively uncommon finding in clinical practice, with a prevalence of 1–5% in all hospitalized patients. However, it is an adverse prognostic marker for mortality and morbidity. Although the correlation between serum phosphate levels and symptoms is not linear,1 severe hypophosphatemia is important to recognize and treat since it can lead to rhabdomyolysis, haemolysis, respiratory failure secondary to diaphragmatic weakness and neurological abnormalities.1–3 We report a case of spurious hypophosphatemia in a patient with longstanding MGUS coincident with the onset of Waldenstrom’s macroglobulinemia due to paraprotein interference with the phosphate assay used. Clinicians should be aware of the possibility of spurious phosphate measurements in patients with paraproteinemias to avoid unnecessary investigation and intervention.

Case report

A 69-year-old man with chronic kidney disease stage 4 (CKD-4) was admitted after severe hypophosphatemia was found following a routine clinic visit. He reported no new symptoms except occasional postural dizziness despite a serum phosphate level of <0.1 mmol/l. Past medical history included acute renal failure secondary to biopsy-proven interstitial nephritis 10 years before, an IgM-Kappa monoclonal gammopathy of undetermined significance (MGUS) detected co-incidently, polymyalgia rheumatica, an abdominal aortic aneurysm repair and degenerative lumbar osteoarthritis. A bone marrow trephine had showed <4% plasma cells and a limited skeletal survey had shown no lytic lesions.

Physical examination on admission was unremarkable. Electrocardiography and chest radiography were reported as normal. Urinalysis revealed +3 albumin, +2 blood, +2 glucose but was negative for ketones and leukocytes. His full blood cell count showed a haemoglobin 10.9 g/dl, white blood cell count 5.8 × 10⁹/l and platelets 221 × 10⁹/l. A serum biochemical profile showed the following: sodium 138 mmol/l, potassium 4.2 mmol/l, calcium 2.31 mmol/l, phosphate <0.1 mmol/l, bicarbonate 27 mmol/l, urea 10.0 mmol/l, creatinine 253 umol/l, total protein 94 g/l, albumin 28 g/l, globulin 66 g/l. Liver function tests were normal. Plasma viscosity was 2.9mPA and parathyroid hormone was 34 pg/ml. Serum protein electrophoresis revealed an IgM-Kappa monoclonal band quantified at 30 g/l. Urine phosphate excretion was not quantified. A bone marrow trephine biopsy was performed. This showed 42% of marrow infiltrated...
## Table 1  Case reports of spurious hypophosphatemia related with hyperglobulinemia

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age</th>
<th>Main diagnosis</th>
<th>Serum globulin analysis</th>
<th>PO4 with routine assay (mmol/l)</th>
<th>PO4 with revised assay (mmol/l)</th>
<th>Bone marrow analysis</th>
<th>Bone scan</th>
<th>Phosphate supplement</th>
<th>Serum creatinine (μmol/l)</th>
<th>Urinalysis</th>
<th>Urinary phosphate excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>80</td>
<td>MM</td>
<td>Monoclonal γ-globulin</td>
<td>&lt;0.32</td>
<td>1.5</td>
<td>NA</td>
<td>NA</td>
<td>Yes</td>
<td>Blood 3+</td>
<td>Protein 3+</td>
<td>672 mmol/24 h</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>53</td>
<td>Bilateral salivary gland swelling</td>
<td>Polyclonal γ-globulin (IgG, IgA, IgM)</td>
<td>&lt;0.32</td>
<td>1.28</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>63</td>
<td>MM</td>
<td>Monoclonal IgGκ</td>
<td>&lt;0.32 to 0.64</td>
<td>1.22</td>
<td>17% plasma cells</td>
<td>NA</td>
<td>Yes</td>
<td>133</td>
<td>Protein 3+</td>
<td>202 -343 mmol/24 h Fractional excretion 57.6%</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>75</td>
<td>MGUS</td>
<td>Monoclonal IgGκ (2.07 g/dl)</td>
<td>&lt;0.32</td>
<td>1.34</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
<td>97</td>
<td>NA</td>
<td>307 mmol/24 h Fractional excretion 14%</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>74</td>
<td>MM</td>
<td>Monoclonal Igκ (4.97 g/dl)</td>
<td>&lt;0.32</td>
<td>2.59</td>
<td>MM</td>
<td>47% plasma cells</td>
<td>yes</td>
<td>yes</td>
<td>201</td>
<td>NA</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>85</td>
<td>MM</td>
<td>Monoclonal Igκ</td>
<td>0.38</td>
<td>1.47</td>
<td>No lytic lesions</td>
<td>yes</td>
<td>yes</td>
<td>159</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>67</td>
<td>NA</td>
<td>Waldenstrom's, MGUS</td>
<td>Monoclonal Igκ (3.43 g/dl)</td>
<td>0.56</td>
<td>1.1</td>
<td>42% lymphoid cells</td>
<td>NA</td>
<td>253</td>
<td>NA</td>
<td>Albumin 3+</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>69</td>
<td>NA</td>
<td>Waldenstrom's, MGUS</td>
<td>Monoclonal Igκ (3.9 g/dl)</td>
<td>&lt;0.32</td>
<td>1.62</td>
<td>No lytic lesions</td>
<td>NA</td>
<td>2+</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*The case reported in this paper. MM: multiple myeloma; NA: not available.*
with small CD20 positive lymphoid cells diagnostic of a low-grade B-cell lymphoma or Waldenstrom’s lymphoplasmacytoid tumour.

In view of the very low phosphate level, he was admitted and given an intravenous phosphate infusion (Polyfusor, 12.6 mmol over 6 h) together with oral phosphate tablets (Phosphate-Sandoz, 96.6 mmol/d). However, he remained asymptomatic throughout and repeat tests of serum phosphate over the following 3 days showed no improvement. The possibility of spurious hypophosphataemia was raised and the sample reanalysed after serial sample dilution. Following this manoeuvre, serum phosphate was quantified as 1.62 mmol/l (reference range 0.78–1.53 mmol/l) with a parallel phosphate level of <0.1 mmol/l by the unmodified assay (ammonium molybdate reaction on the Beckman Synchron LX20 analyser). Oral phosphate replacement was discontinued immediately and the level of serum phosphate remained within normal range following discharge using the modified assay.

### Discussion

Hypophosphatemia is rare in patients with impaired glomerular filtration rate (GFR) since phosphate tends to accumulate due to decreased renal phosphate excretion. Several factors should be considered when hypophosphatemia is detected. These include decreased phosphate intake (decreased intestinal absorption or increased gastrointestinal losses), excess renal phosphate wasting (tubular defects or hyperparathyroidism) or a shift from extracellular to intracellular compartments (secondary to alkalosis).4,5 We suggest that the possibility of spurious hypophosphatemia should also be considered.

Spurious hypophosphatemia is a rare finding in hypergammaglobulinemic patients (summarized in Table 1). Although the majority of cases reported were related to monoclonal paraproteins (IgGκ, IgGλ, IgAκ, IgMκ), a case of polyclonal hypergammaglobulinemia (IgG, IgA, IgM) has also been reported.6 Our case was unusual in that it was also the presenting sign of undetected Waldenstrom’s macroglobulinemia on a background of long-standing MGUS.

The properties that lead to occasional paraprotein interference with the phosphate assay remain uncertain but may relate to unique charge characteristics or other physicochemical properties.7 Possible mechanisms include direct binding to inorganic phosphate, protein precipitation in distilled water or interference with the stabilization of phosphomolybdate used in many automatic autoanalysers as a chromogenic substrate.6,7 Spurious hyperphosphatemia associated with hypergammaglobulinemia has also been reported in some patients.8 Why some paraproteins are associated with high rather than low serum phosphate levels remains unknown. Rare cases of renal phosphate wasting due to direct tubular effects of monoclonal paraproteins have also been reported.9 Measurement of a 24 h urine phosphate excretion should exclude this possibility.

The possibility of spurious phosphate estimations should be suspected in patients with known or newly presenting paraproteinemias. Accurate phosphate determinations rely on removing the excess paraprotein by deproteinization, including a detergent in the sample buffer to prevent protein precipitation or adding a reducing agent to stabilize the phosphomolybdate colour complex. Simple serial dilution of the sample (as in our patient) may be sufficient to correct the abnormality but does not work in all cases.

### References


