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CASE REPORT

Severe hyperphosphatemia in a patient with chronic kidney disease and multiple myeloma–to strengthen the case toward renal replacement therapy?

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Key Clinical Message

We report a patient with multiple myeloma and chronic kidney disease who presented with severe hyperphosphatemia in the outpatient clinic without any related symptoms. Initial differential diagnosis: Tumor lysis syndrome or chronic kidney disease. Further work-up revealed pseudohyperphosphatemia. In general, treatment is not necessary if the true phosphate level is within the reference range and the patient is asymptomatic.

Keywords

Chronic kidney disease, hyperphosphatemia, multiple myeloma, pseudohyperphosphatemia.

Multiple myeloma is a disease requiring multidisciplinary approach–mostly oncologists and nephrologists are involved. Here we describe a 62-year-old male patient with multiple myeloma (IgG Kappa) (diagnosis 2006). Treatment with Vincristin, Doxorubicin, and Dexamethason was started. Restaging revealed evidence of progression of myeloma. Therefore, autologous hematopoietic stem cell transplantation was performed, leading to complete remission. Two years later, there was progression of myeloma and multiple chemotherapy regimens were administered up to now (cyclophosphamide, thalidomide, lenalidomide, bendamustine). At time of presentation in the outpatient clinic, the patient had no complaints except diarrhea for a few days. Abnormal laboratory findings at presentation were strongly increased phosphorus level, elevated serum creatinine of 2.3 mg/dL (estimated glomerular filtration rate (GFR), calculated using MDRD (Modification of Diet in Renal Disease) Study equation was 31 mL/min per 1.73 m^2), and pancytopenia. Chronic kidney disease due to myeloma was diagnosed several months ago. Serum immunofixation electrophoresis revealed elevated IgG and K:λ ratio was 185.2 (normal range adapted to patients with impaired kidney function 0.37–3.1). In addition, total serum protein concentration was strongly increased. Urinary studies showed spot urine protein to creatinine ratio of 0.13 g/g (normal range <0.25 g/g). Significant laboratory findings are shown in Table 1. The patient did not report symptoms or signs of hyperphosphatemia and he denied neither using any dietary protein supplements or phosphate soda preparation nor having excessive dairy product intake in the recent past. At this stage, a nephrologist was contacted with the question whether renal replacement therapy due to severe acute hyperphosphatemia should be started. In steady state, the kidney primarily determines serum phosphate concentration by excretion of dietary phosphate. There are three general circumstances in which phosphate entry into the extracellular fluid exceeds the degree to which it can be excreted resulting in hyperphosphatemia: acute or chronic kidney disease, massive acute phosphate load, and primary increase in tubular phosphate reabsorption. Reduction in GFR results in diminished phosphate filtration and excretion. Initially, phosphate balance could be maintained by decreased proximal phosphate reabsorp-

Table 1. Laboratory findings at outpatient clinic.

Parameter	Units	Reference values
Phosphate	8.6 mmol/L	0.68–1.68 mmol/L
Creatinine	2.3 mg/dL	0.5–1.4 mg/dL
Calcium	2.18 mmol/L	2.05–2.55 mmol/L
Lactate dehydrogenase	176 U/L	<176 U/L
Uric acid	8.8 mg/dL	3.5–8.5 mg/dL
IgG	7502 mg/dL	700–1600 mg/dL
Serum protein concentration	11.8 g/dL	6.5–8.2 g/dL
Albumin	2.5 g/dL	3.5–5.0 g/dL

tion. The GFR of our patient was 31 mL/min and kidney function had remained stable over the last few months. Therefore, severe hyperphosphatemia could not exclusively be explained by impaired kidney function. Either exogenous or endogenous sources might cause massive acute phosphate load. Phosphate is an intracellular ion and therefore it could be released into extracellular fluid due to marked tissue breakdown, causing symptomatic hypocalcemia. The phosphorus concentration in malignant cells is higher than in normal cells and rapid tissue breakdown often leads to acute hyperphosphatemia including an increased risk of calcium phosphate precipitation in the renal tubules leading to acute kidney failure [1]. It is noteworthy, that tumor lysis syndrome (TLS) is less common in multiple myeloma [2] and in our patient, uric acid was only slightly elevated, lactate dehydrogenase and calcium levels were within the normal range, arguing against TLS as reasons for hyperphosphatemia (Table 2 shows differential diagnosis of hyperphosphatemia). Due to these findings, additional investigations were performed. The patient's initial blood sample was tested as previously described [3] 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 complex absorbs light and is quantified photometrically in the ultraviolet range (wavelength 340 nm). Light absorbance is directly proportional to the inorganic phosphorus concentration [3]. Due to concern about pseudohyperphosphatemia the samples were analyzed in a second step using simple dilution of the samples to eliminate turbidity and interference (1:5 and 1:10) as previously described [4–6]. Afterward, phosphate levels decreased to still slightly elevated levels of 1.82 mmol/L (normal range 0.68–1.68 mmol/L), which is explained by the chronic kidney disease. During follow-up, the phosphate levels remained stable.

Two explanations exist regarding pseudohyperphosphatemia. The first explanation comprised the hypothesis that pseudohyperphosphatemia is caused by direct binding of paraproteins to phosphorus, whereas the other hypothesis postulated that paraproteins bind to molybdate resulting in turbidity. During analysis, the turbid reaction mixture scatters and adsorbs light while reducing its transmittence. This might be interpreted as falsely high phosphorus level [3, 7, 8]. Most reported cases of patients with myeloma and pseudohyperphosphatemia had normal kidney function, which leads to the diagnosis of pseudohyperphosphatemia much more easily [3, 9], whereas our patient had impaired kidney function. In general, treatment is not necessary if the true phosphate level is within the reference range and the patient is asymptomatic [3].

Table 2. Differential diagnosis of hyperphosphatemia and pseudohyperphosphatemia.

Impaired kidney function resulting in reduced phosphate excretion
- Acute kidney disease
- Chronic kidney disease
Massive acute phosphate load
• Endogenous
- Tumor lysis syndrome
- Lactic acidosis
- Ketoacidosis
• Exogenous
- Ingestion of large amount of phosphate-containing laxatives
Increased tubular reabsorption of phosphate
- Hypoparathyroidism
- Acromegaly
- Bisphosphonates
- Vitamin D toxicity
- Familial tumoral calcinosis
Pseudohyperphosphatemia due to interference with analytical methods
- Hyperglobulinemia
• Multiple myeloma
• Waldenström's macroglobulinemia
• Monoclonal gammopathy
- Hyperlipidemia
- Hemolysis
- Hyperbilirubinemia
- Drugs
• High-dose liposomal amphotericin B
• Sample contamination with recombinant tissue plasmin activator or heparin

This case illustrates the course of pseudohyperphosphatemia in a patient with myeloma and chronic kidney disease. Especially oncologists and nephrologists should be aware of pseudohyperphosphatemia leading to prompt identification of these patients and mitigate unnecessary treatment.

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None.

Conflict of Interest

None declared.

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