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Case Report

Long-term Evolution of Hypophosphatemia and Osteomalacia in a Patient With Multiple Myeloma

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Abstract

Multiple myeloma commonly manifests with symptoms arising from the involvement of various organs, particularly the bone and kidneys. In this report, we detail the case of a 44-year-old man who was diagnosed with multiple myeloma associated with reduced bone density. He exhibited clinical findings of osteomalacia due to Fanconi syndrome (characterized clinically by bone pain and proximal weakness and biochemically by elevated serum alkaline phosphatase, hypophosphatemia, hypouricemia, and glucosuria). With phosphate replacement, there was a notable improvement in bone pain, osteomalacia, and bone mineral density. Nevertheless, the patient continued to experience renal wasting of phosphate, uric acid, and glucose despite achieving remission from multiple myeloma for nearly 2 years. Our case highlights several important clinical features of myeloma-associated Fanconi syndrome, including the need to recognize this complication to appropriately treat the underlying bone disease while avoiding osteoclast inhibitors and the long-term persistence of the proximal renal tubulopathy despite achieving remission from myeloma and correction of osteomalacia.

Key Words: multiple myeloma, osteomalacia, proximal tubulopathy, fanconi syndrome, hypophosphatemia

Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by uncontrolled proliferation and accumulation of monoclonal malignant plasma cells in the bone marrow that produce large amounts of abnormal light chains. Patients with MM generally present with either anemia, lytic bone lesions, hypercalcemia, and/or kidney injury.

Light chain proximal tubulopathy is a rare complication of MM. In this condition, light chains accumulate in the kidneys and cause damage to the proximal tubules. Proximal tubulopathy can result in a range of abnormalities, including low levels of phosphate in the blood, either alone,[1] or in combination with metabolic acidosis, and renal failure. Treatment typically involves aggressive management of the underlying MM with chemotherapy and immunomodulatory drugs.

This manuscript presents a unique case of MM, characterized by prolonged hypophosphatemia and persistent signs of proximal renal tubulopathy even after remission from MM had been achieved.

Case Presentation

A 44-year-old Asian man presented in October 2020 with generalized weakness accompanied by an unintentional weight loss of 30 lb over the preceding 8 months. The patient's past medical history was significant for bilateral carpal tunnel surgery and nonnephrotic proteinuria for 7 years for which he was taking an angiotensin-converting enzyme inhibitor. Physical examination was notable for increased tongue thickness and scalloping. He exhibited normal serum calcium and creatinine, but severe proteinuria (10 815 mg/day, reference range: <300 mg/day) was found in his 24-hour urine. Urine protein electrophoresis was positive for monoclonal gammopathy (albumin 8.5%; 234.0 mg/dL paraprotein band, reference range: none), and serum protein electrophoresis showed a gamma monoclonal spike of 0.2 g/dL (reference range: none).

On further investigations, he had elevated serum beta-2 microglobulin levels at 3.26 mcg/mL (reference range: 1.21-2.70 mcg/mL); the serum kappa free light chain concentration was measured at 286.23 mg/L (reference range: 3.30-19.40 mg/L), and the kappa:lambda light chain ratio was 43.90 (reference range: 0.26-1.65). A bone marrow biopsy showed the presence of 40% to 50% neoplastic plasma cells. Moreover, the fluorescence in situ hybridization panel analysis exhibited abnormalities, including immunoglobulin heavy chain / musculoaponeurotic fibrosarcoma (IGH/MAF) [t(14; 16)], an extra copy of chromosome 1q, and deletion of the long arm of chromosome 13. The Congo red staining in the bone marrow biopsy yielded negative results for amyloid deposition. However, in an abdominal fat pad biopsy, the Congo red staining was positive, with green birefringence observed upon polarization. As a result of these findings, a diagnosis of both MM and systemic kappa light chain AL amyloidosis was established. A skeletal survey showed diffuse osteopenia without any fracture or lytic bone lesions. The patient underwent treatment for MM with 5 cycles

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Table 1. Temporal evolution of blood and urine parameters

Date	12/2020	6/2021	10/2021	6/2022	1/2023	6/2023	Reference range
Blood parameters							
BUN	8 mg/dL (2.85 mmol/L)	4 mg/d (1.43 mmol/L)	8 mg/dL (2.85 mmol/L)	7 mg/dL (2.5 mmol/L)	7 mg/dL (2.5 mmol/L)	6 mg/dL (2.14 mmol/L)	6–23 mg/dL (2.14–8.21 mmol/L)
Creatinine	1.03 mg/dL (91 μmol/L)	0.85 mg/dL (75 μmol/L)	0.88 mg/dL (77 μmol/L)	1.12 mg/dL (99 μmol/L)	1.07 mg/dL (94 μmol/L)	1.01 mg/dL (89 μmol/L)	0.72–1.25 mg/dL (64–111 μmol/L)
Sodium	137 mmol/L	140 mmol/L	137 mmol/L	138 mmol/L	136 mmol/L	136 mmol/L	135–145 mmol/L
Potassium	3.9 mmol/L	3.9 mmol/L	3.6 mmol/L	4.3 mmol/L	3.5 mmol/L	3.7 mmol/L	3.6–5.0 mmol/L
Chloride	107 mmol/L	109 mmol/L	108 mmol/L	104 mmol/L	108 mmol/L	109 mmol/L	98–109 mmol/L
Bicarbonate	21 mmol/L	24 mmol/L	21 mmol/L	25 mmol/L	23 mmol/L	20 mmol/L	22–31 mmol/L
Calcium	9.4 mg/dL (2.34 mmol/L)	9.1 mg/dL (2.27 mmol/L)	9.2 mg/dL (2.29 mmol/L)	9.9 mg/dL (2.47 mmol/L)	9.2 mg/dL (2.29 mmol/L)	8.8 mg/dL (2.19 mmol/L)	8.4–10.2 mg/dL (2.10–2.54 mmol/L)
Magnesium	2.6 mg/dL (1.06 mmol/L)	2.2 mg/dL (0.90 mmol/L)	2.3 mg/dL (0.94 mmol/L)	2.7 mg/dL (1.11 mmol/L)	2.2 mg/dL (0.90 mmol/L)	2.1 mg/dL (0.86 mmol/L)	1.6–2.6 mg/dL (0.66–1.07 mmol/L)
Phosphorous	1.8 mg/dL (0.58 mmol/L)	2.3 mg/dL (0.74 mmol/L)	1.9 mg/dL (0.61 mmol/L)	3.2 mg/dL (1.03 mmol/L)	2.2 mg/dL (0.70 mmol/L)	1.9 mg/dL (0.61 mmol/L)	2.4–4.5 mg/dL (0.77–1.45 mmol/L)
Uric acid	1.1 mg/dL (0.065 mmol/L)	— —	1.5 mg/dL (0.089 mmol/L)	1.5 mg/dL (0.089 mmol/L)	1.9 mg/dL (0.113 mmol/L)	1.4 mg/dL (0.083 mmol/L)	3.4–7.2 mg/dL (0.202–0.428 mmol/L)
Alkaline phosphatase	221 IU/L	178 IU/L	459 IU/L	131 IU/L	132 IU/L	139 IU/L	40–150 IU/L
glucose	168 mg/dL (9.3 mmol/L)	96 mg/dL (5.3 mmol/L)	69 mg/dL (3.8 mmol/L)	82 mg/dL (4.6 mmol/L)	93 mg/dL (5.2 mmol/L)	95 mg/dL (5.3 mmol/L)	70–139 mg/dL (3.9–7.7 mmol/L)
25-hydroxyvitamin	— —	— —	45.3 ng/mL (113 nmol/L)	61.8 ng/mL (154 nmol/L)	53.8 ng/mL (134 nmol/L)	39.2 ng/mL (97 nmol/L)	30–80 ng/mL (75–200 nmol/L)
1,25-dihydroxyvitamin D	— —	— —	64 pg/mL (159 pmol/L)	69 pg/mL (172 pmol/L)	64 pg/mL (159 pmol/L)	62 pg/mL (154 pmol/L)	18–64 pg/mL (50–160 pmol/L)
PTH	— —	20.8 pg/mL (2.2 pmol/L)	17.1 pg/mL (1.8 pmol/L)	22.0 pg/mL (2.3 pmol/L)	24.9 pg/mL (2.6 pmol/L)	35 pg/mL (3.7 pmol/L)	15–77 pg/mL (1.6–8.2 pmol/L)
FGF-23	—	—	<14 pg/mL	<14 pg/mL	<14 pg/mL	<14 pg/mL	≤59 pg/mL
Free kappa LC	304.45 mg/L	14.34 mg/L	11.44 mg/L	25.57 mg/L	35.45 mg/L	32.54 mg/L	3.30–19.40 mg/L
Free lambda LC	3.82 mg/L	7.78 mg/L	8.26 mg/L	16.05 mg/L	18.85 mg/L	17.35 mg/L	5.71–26.30 mg/L
24-hour urine parameters							
Protein	—	—	1730mg/day	3998 mg/day	551 mg/day	608 mg/day	<300 mg/day
pH	—	—	7.32	7.26	—	7.28	5.5–7.5

(*continued*)

Table 1. Continued

Date	12/2020	6/2021	10/2021	6/2022	1/2023	6/2023	Reference range
Calcium	—	—	328 mg/day (8.2 mmol/day)	452 mg/day (11.3 mmol/day)	—	309 mg/day (7.7 mmol/day)	100–250 mg/day (2.5–6.25 mmol/day)
	—	—			—		
Creatinine	—	—	970 mg/day (8.5 mmol/day)	1156 mg/day (10.2 mmol/day)	—	932 mg/day (8.2 mmol/day)	10–25 mg/kg/day
	—	—			—		
Phosphorus	—	—	455 mg/day (14.6 mmol/day)	863 mg/day (27.8 mmol/day)	—	647 mg/day (20.8 mmol/day)	<1100 mg/day (<35.5 mmol/day)
	—	—			—		
Calculated parameters (%)							
FE Phosphate	—	—	36	26	—	26	—
FE uric acid	—	—	38	43	—	51	—
FE glucose	—	—	8.6	—	—	5.8	—

Abbreviations: BUN, blood urea nitrogen; FE, fractional excretion; FGF-23, fibroblast growth factor-23; LC, light chain.

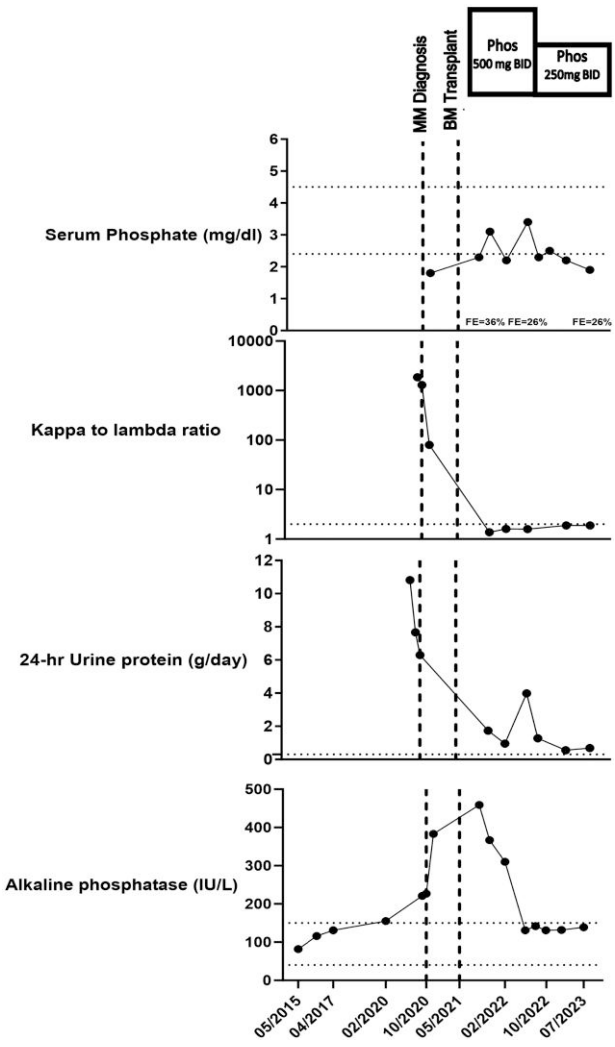

Figure 1. Longitudinal variations in serum phosphate, alkaline phosphatase, proteinuria, and the kappa:lambda ratio. Vertical dashed lines denote significant time points, such as the diagnosis of multiple myeloma and date of stem cell transplantation. The horizontal dashed lines represent the reference range for each parameter. The boxes above the graph indicate the duration and dose of potassium phosphate-sodium phosphate supplementation (Phos).

of a combination of chemotherapy (daratumumab, cyclophosphamide, dexamethasone, and bortezomib), followed by stem cell transplantation in May 2021.

Despite significant improvement in the kappa:lambda ratio and remission from MM, he experienced worsening bone pain and proximal muscle weakness starting in the second quarter of 2021. Additional studies showed high alkaline phosphatase (ALP) levels of 459 (reference range: 40-150 IU/L) (81.6% from bone; reference range: 19.1-67.7%) and significant hypophosphatemia of 1.9 mg/dL (0.58 mmol/L) (reference range: 2.4-4.5 mg/dL; 0.77-1.45 mmol/L), which was determined to be caused by renal phosphate wasting (inappropriately high fractional excretion of phosphate; 36%). The patient also exhibited hypouricemia (1.5 mg/dL; 0.089 mmol/L; reference range: 3.4-7.2 mg/dL; 0.202–0.428 mmol/L) with elevated fractional excretion of uric acid (38%) and glucosuria despite normal blood glucose levels, compatible with generalized renal proximal tubular wasting. Notably, serum calcium, creatinine, parathyroid hormone, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin

D were within normal ranges, while serum intact fibroblast growth factor 23 (FGF-23, measured by enzyme-linked immunosorbent assay kit; MedFrontier intact FGF-23; Eagle Biosciences, Amherst, NH, USA) was suppressed, and 24-hour urine calcium was elevated (Table 1). A baseline dual energy X-ray absorptiometry scan revealed a Z-score of −5.0 at the lumbar spine and −4.2 at the left femoral neck.

Diagnostic Assessment

Based on the clinical presentation of proximal weakness and bone pain, along with the laboratory findings of hypophosphatemia and elevated serum ALP and the very low bone mineral density, the patient was diagnosed with osteomalacia secondary to hypophosphatemia from renal phosphate wasting presumably caused by light chain proximal tubulopathy.

Treatment

Initially, to treat his osteomalacia, he was prescribed calcitriol 0.25 mcg daily and potassium phosphate-sodium phosphate 500 mg twice daily.

Outcome and Follow-up

Over the subsequent months, he experienced significant improvement in bone pain and proximal weakness, as well as in his serum phosphorus and ALP levels (Fig. 1), leading to calcitriol discontinuation within 4 months of initiation and a reduction in the dosage of the phosphate preparation to 250 mg twice daily ~ 10 months after initiation.

Over the subsequent 21 months, he exhibited normalization in serum ALP and a significant improvement in bone mineral density, with Z-scores at the spine and left femoral neck improving to −2.2 and −1.1, respectively (Table 2). However, serum phosphate and uric acid levels have remained persistently low throughout the 2-year follow-up period (Table 1), suggesting persistent renal proximal tubular defect, and his hypercalciuria has persisted.

Discussion

We hereby present a patient with MM who suffered from proximal tubulopathy characterized by hypophosphatemia, glucosuria, proteinuria, and hypouricemia and manifested clinically with proximal muscle weakness and osteomalacia. Over the 2 years following his remission from MM, his osteomalacia and bone mineral density improved significantly with phosphate supplementation, but his proximal tubulopathy persisted.

Renal impairment is a common manifestation of MM, with serum creatinine elevation noted in approximately half of the patients at diagnosis.[2,3] The accumulation of light chains in the kidneys can lead to several types of kidney injury, including cast or crystalline nephropathy, amyloidosis, and monoclonal immunoglobulin deposition disease, which lead to proteinuria, reduced kidney function, and eventually kidney failure.[4,5] The most commonly diagnosed form of kidney injury in a patient with MM is cast nephropathy, which leads to intratubular obstruction from the precipitation of free light chain in the lumen of the distal nephron, which leads to interstitial inflammation and fibrosis.[6] The severity of kidney injury in MM patients is often determined by the level of light chain production and the type of light chain involved. Patients with high levels of light chain production, particularly those with kappa light chains, are at a higher risk for kidney injury. Additionally, patients with hypercalcemia, infection, dehydration, and/or other comorbidities may be more susceptible to kidney injury from light chains.[7]

In recent years, reports of plasma cell dyscrasias damaging the proximal tubule and presenting clinically with hypophosphatemia, hypouricemia, glucosuria, and bone diseases like osteomalacia have been described.[8,9] Most of those cases recovered after MM treatment and remission or were lost to follow-up. We have so far followed our patient for nearly 2 years since going into remission after bone marrow transplantation and, despite normalization of ALP level and resolution of his osteomalacia clinically and radiographically, his proximal tubulopathy including hypophosphatemia, hypouricemia, and proteinuria have persisted. His persistently suppressed serum FGF-23 is likely in response to persistent hypophosphatemia and may be contributing to the high-normal serum 1,25-dihydroxyvitamin D and the associated hypercalciuria (Fig. 2).

Free light chains may be toxic to the proximal tubule directly by blocking the transport of substrates like glucose and amino acids, or free light chains endocytosis can induce a spectrum of inflammatory effects that lead to release of inflammatory and profibrotic cytokines, such as interleukin-6, interleukin-8, and transforming growth factor-β1 that can trigger apoptotic pathways in the proximal tubule.[6]

In MM, bone-disease-related lesions are one of the most common features. Over 80% of newly diagnosed MM patients will develop detectable bone disease.[10] Plasma cells produce both osteoclast-activating and osteoblast-inhibiting factors that result in decreased expression of ALP and collagen type I with net bone resorption.[11] This generally results in lytic bone lesions and/or diffuse osteopenia. Recent investigations have indicated that blood ALP levels in MM may be low or normal even when bone lesions are present, unlike other malignancy-related bone lesions where it tends to be high.[12] Therefore, it becomes essential to examine the reason behind elevated ALP in MM, as such elevation may be a manifestation of hypophosphatemic osteomalacia.

Zoledronic acid is a potent bisphosphonate that has shown anti-MM activity besides its antiresorptive action. It has therefore become a mainstay treatment of bone disease in MM.[13] In fact, administering bisphosphonates to all patients with active MM is recommended regardless of the presence of bone lesions.[14] However, we feel it is essential to distinguish osteomalacia from other causes of low bone density in MM. Combining osteomalacia with bisphosphonate treatment can result in profound hypocalcemia and hypophosphatemia, which can exacerbate the condition.[15] Therefore, proper evaluation and diagnosis are crucial before initiating any bisphosphonate treatment to ensure effective management and minimize potential complications.

Table 2. Temporal evolution of bone density results

Date	10/2021	6/2023
Lumbar spine BMD	0.612 g/cm^2	0.938 g/cm^2
Lumbar spine Z-score	−5.0	−2.2
Femoral neck BMD	0.458 g/cm^2	0.752 g/cm^2
Femoral neck Z-score	−4.2	−1.1

Abbreviations: BMD, bone mineral density.

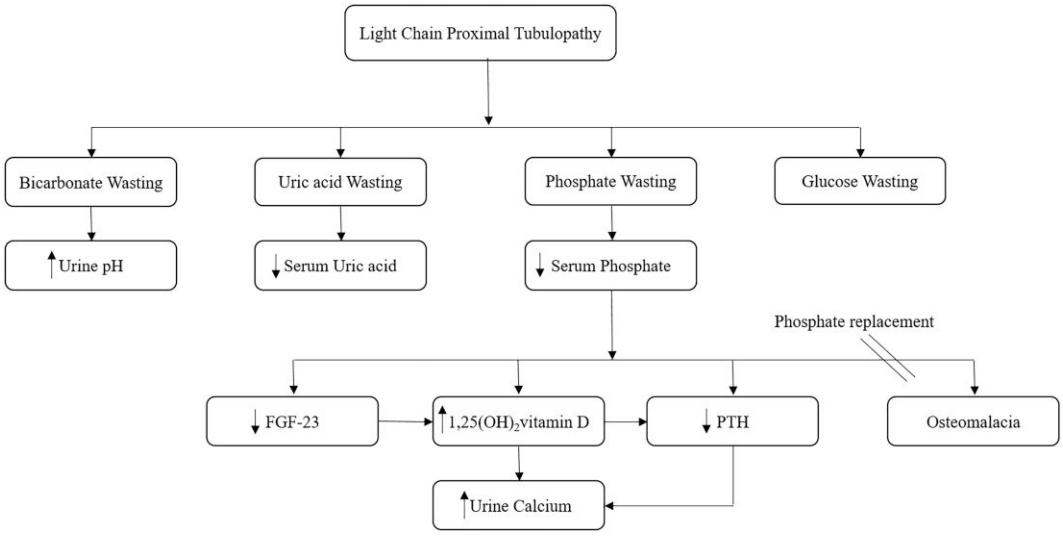

Figure 2. Mineral and electrolyte changes resulting from light chain proximal tubulopathy.

In summary, we have presented the case of a patient with MM complicated by hypophosphatemic osteomalacia from renal phosphate wasting presumably caused by light chain proximal tubulopathy. His clinical course was characterized by resolution of osteomalacia with phosphate supplementation but persistent tubulopathy characterized by hypophosphatemia, glucosuria, proteinuria, and hypouricemia 2 years after achieving remission from MM.

Learning Points

- MM can present with hypophosphatemic osteomalacia due to myeloma-induced renal proximal tubular dysfunction resulting in renal phosphate wasting, suppressed serum FGF-23 levels, alongside an elevated serum 1,25-dihydroxyvitamin D, differentiating it from FGF-23-mediated tumor-induced osteomalacia.
- Our case highlights that myeloma-induced proximal tubular dysfunction can be long lasting despite remission from multiple myeloma, while osteomalacia can be treated with phosphate supplementation.
- It is essential to differentiate between osteomalacia and osteoporosis in patients with myeloma.
- Physicians should avoid prescribing bisphosphonates before ruling out osteomalacia, particularly when the serum ALP level is elevated.

Contributors

Both authors made significant contributions to the writing and submission of the manuscript. N.M.M. evaluated and treated the patient. A.Z. drafted the initial version of this manuscript. The final draft was reviewed and approved by both authors.

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Disclosures

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Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient.

Data Availability Statement

Original data generated and analyzed during this study are included in this published article.

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