Case Report

Hypophosphatemic osteomalacia due to cadmium toxicity in silverware industry: A curious case of aches and pains

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Abstract

Hypophosphatemic osteomalacia in an adult often gives clinical diagnostic challenges. Usually, they are caused by either tumor-induced osteomalacia or due to genetically mediated hypophosphatemia, particularly X-linked hypophosphatemia. However, heavy metal toxicity, leading to global proximal renal tubular dysfunction, is a rare cause, and in particular, cadmium toxicity is rarely encountered in clinical practice. The presence of bony pain and neurological deficit, along with a classical exposure history, provides the diagnostic clue. In this background, here we present a middle-aged man who had severe bony pains all over his body and lower back stiffness for five years. He underwent an initial workup as a suspected spondyloarthropathy but was later on, found to have hypophosphatemic osteomalacia and severe proximal renal tubular dysfunction. Further, the workup revealed elevated FGF-23. His occupational history revealed prolonged exposure to cadmium fumes in the silverware industry. He improved moderately with treatment; however, significant renal damage is still present. This case highlights the importance of considering cadmium toxicity in proper clinical and occupational contexts in the evaluation of hypophosphatemic osteomalacia in an adult.

Keywords: Cadmium, heavy metal, hypophosphatemia, nephropathy, osteomalacia

Introduction

Hypophosphatemic osteomalacia in an adult can often present with diagnostic and therapeutic challenges. Frequently, the causes of chronic hypophosphatemia are either genetic or acquired and either fibroblast growth factor-23 dependent or independent.[1] Apart from various common etiologies, an acquired Fanconi-like phenotype with proximal tubular dysfunction can present similarly. Among the causes of proximal tubular dysfunction, heavy metals remain an essential consideration but are not routine in endocrinological practice. Mainly, cadmium toxicity is notorious for this type of presentation. The conglomeration of musculoskeletal and renal effects of cadmium toxicity has been known for decades in countries like Japan.[2] It is a significant cause of mortality and morbidity in the exposed population. However, the silverware industry is a small-scale household-level industry in India, where cadmium exposure is extensive among silversmiths, and this is reflected by two earlier reports from India.[3,4] In this background, we report a case of cadmium toxicity, which presented as a clinical challenge and was misdiagnosed initially.

Case Presentation

A male patient in his early 40s visited the endocrinology outpatient clinic with a history of dull aches and pains all over the body. Ten years ago, he started developing vague, dull, aching pains in the lower back region, requiring intermittent analgesic use. However, the severity has increased over the last five years, and the patient has been unable to walk independently recently. He also developed significant muscle weakness around the hip and had a history of recurrent falls over the last two years. He

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also complained of intermittent pain at various small and large joints without any specific pattern or inflammatory changes. However, there was no history of any fracture or tetany. No history is suggestive of hearing loss, visual disturbances, or dental abnormality was present. There were no changes in teeth except dental caries.

He has been under care from different hospitals for the last five years and underwent investigations for a possible unclassified spondyloarthropathy or rheumatological disease. Nevertheless, all his investigations were routine, including anticyclic citrullinated peptide antibody and HLA B27 screening, albeit an elevated rheumatoid factor (RA factor 110 IU/ml; normal range <5.00; immunoturbidometric assay) was seen. The clinical examination revealed spasticity in the lower limb muscles with normal reflexes, thus invoking a diagnosis of possible hereditary spastic paraplegia also. Consequently, he underwent magnetic resonance imaging of the cervical region, revealing a postero-central osteophytic bulge, which was possibly the extensive enthesopathy changes that were missed. Moreover, mildly elevated creatinine (1.36 mg/dl) and an elevated urinary spot albumin/creatinine ratio (378 mg/g of creatinine; normal <30) back in 2018 were not worked up thoroughly.

During his current evaluation, he was found to have mild hypokalemia, hypophosphatemia, and low normal parathyroid hormone levels (iPTH). At the same time, other biochemical investigations were normal except for mild hypochromic microcytic anemia [See Table 1]. He also had elevated creatinine (1.6 mg/dl). His ratio of maximum tubular reabsorption of phosphate (TmP) to glomerular filtration rate (GFR) (TmP/GFR) was low (2.4 mg/dl; normal 2.5–4.5), suggestive of renal phosphaturia. He also had elevated urine protein, calcium, glucose, uric acid, and hypouricemia [see Table 1]. This was suggestive of severe generalized proximal renal tubular dysfunction, which was acquired. However, his serum bicarbonate was borderline low. He also had a high C-terminal fibroblast growth factor (FGF-23) level. (311 RU/ml, normal up to 150; performed by ELISA). He had a remarkably high 24-h urinary beta-two microglobulin [Table 1].

Table 1: Various biochemical parameters are shown in Table 1

Parameter (Normal range)	Observed value
Serum calcium (8.5–10.2 mg/dl)	8.8
Serum albumin (3.5–5.0 g/dl)	4.5
Serum phosphorus (2.5–4.5 mg/dl)	2.4
TmP/GFR (2.5–4.5 mg/dl)	2.4
Serum 25-OH Vitamin D3 (30–100 ng/dl)	30.45
Intact PTH (12–88 pg/ml)	17.26
C-terminal fibroblast growth factor-23 (FGF-23) (up to 150 RU/ml)	311
Serum potassium (3.5–5.1 mEq/L)	3.2
Serum magnesium (1.6–2.6 mg/dl)	2.3
Serum creatinine (0.6–1.2 mg/dl)	1.6
Serum alkaline phosphatase (53–128 U/L)	267
Serum bicarbonate (22–28 mmol/L)	20
Serum uric acid (3.5–8.5 mg/dl)	1.9
24-h urinary calcium (up to 300 mg/24 h)	352
Urinary protein/creatinine ratio (mg/g of creatinine)	6778
24-h urinary beta 2 microglobulin (<300 ng/mL)	60421
24-h urinary cadmium (0.0–3.3 µg/24 h)	51.1
Plasma cadmium (0.0–5.0 µg/L)	30.44

His radiographs revealed pseudo-fractures at different bones, including the right femoral shaft, tibia, ulna, and a few old healed pseudo-fractures [Figure 1 panel 1; A, B]. Further, he had evidence of extensive enthesopathy in the pelvis, ankle region, along the lumbar spine, along with osteopenia [Figure 1 panel 1; C]. He also had altered corticomedullary differentiation in the kidney, suggestive of medical renal disease, and small renal calculus at the renal pelvis without any nephrocalcinosis in the ultrasonographic examination. No abnormality was detected in the cardiac or hepatic function during this admission.

Considering the potential historical clue of musculoskeletal symptoms and proximal renal tubular dysfunction, a further inquiry into his history was made. He revealed that he had been working at a silver jewelry factory since he was 15 years old and had stopped working for the last two years due to current illnesses. He had extensive exposure to inhalational cadmium fumes for over 15 years. Furthermore, a review of the old investigations showed a persistently low phosphorus and a low iPTH [see Table 2]. Considering this occupational exposure, a diagnosis of heavy metal poisoning was considered. His whole blood cadmium was 30.44 mg/L (normal 0.0–5.0), and 24-h urinary cadmium was 51.1 mg (normal 0.00–3.3) (method: Inductively coupled plasma mass spectrometry, ICPMS). Finally, a diagnosis of hypophosphatemic osteomalacia due to severe cadmium toxicity was made.

He was started on oral phosphate granules at 50 mcg/kg/day in four doses: activated vitamin D, calcitriol (0.25 mg twice daily), and oral potassium citrate. He was further advised to decrease cadmium exposure ultimately. After six months of follow-up, he has shown healing in the pseudo-fracture [see Figure 1C, panel 1], but he had developed further pain and swelling in the right knee. It was found to be non-inflammatory pain with minimal effusion and improved by analgesics and supportive care. His biochemical parameters are somewhat normalized after six months of treatment [see Table 2], but the clinical improvement has been modest.

Discussion

We have reported a case of hypophosphatemic osteomalacia due to long-term exposure to cadmium in the silverware industry. The case summarizes that a diligent search for etiological factors in hypophosphatemic osteomalacia is required, often with good rewards. In this case, the clinching point was his occupational history, albeit the diagnosis was elusive for five years.

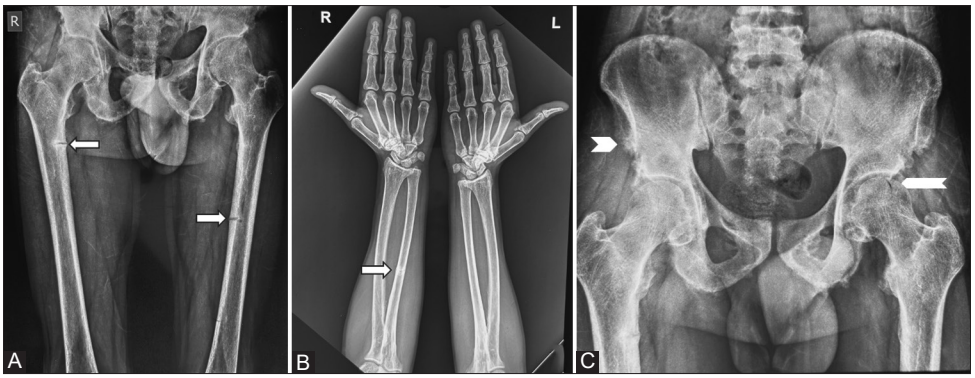

Figure 1: X-ray of the pelvis and forearm showing pseudo-fracture due to hypophosphatemia (Panels A and B, respectively) and extensive enthesopathy in the pelvis (Arrowhead, C panel)

Table 2: Follow-up data of selected variables is shown in Table 2

Parameters	5 years back	On admission	6-month follow-up
Serum creatinine	1.32	1.6	1.35
Vitamin D3	19.92	30.45	–
iPTH	11.9	17.26	–
Serum calcium	9.4	8.8	9.0
Serum phosphorus	2.5	2.4	3.1
Serum potassium	3.2	3.2	3.8

Heavy metal exposure, particularly cadmium exposure, has many clinical consequences. The toxic effect of cadmium on the musculoskeletal system and renal proximal tubule function was recognized earlier in the Jinzu River basin in Toyama, Japan, where the disease is known as itai–itai disease, literally meaning "ouch-ouch."[2,5] Cadmium exposure usually occurs through contaminated food or water, either accidentally or through occupation, accumulating in the body for 25–30 years. Cadmium exposure produces toxic effects on bone and kidneys,[2,5] the liver, the development of certain types of malignancies, and the deterioration of cardiovascular health.[6,7] Low-level cadmium exposure can directly affect bone, increasing the risk of osteoporosis and fracture in both women and men.[8,9]

Earlier in India, Paul J and colleagues[3] reported three cases with similar presentations with exposure to cadmium through the silverware industry. However, our patient had elevated FGF-23 levels compared to the patients of J Paul and colleagues, where two patients had normal FGF-23 levels. Hypouricemia, as a part of proximal tubular dysfunction, seems universal and can serve as a potential clue in the diagnostic workup of hypophosphatemia. Moreover, despite normal serum albumin in a hypophosphatemic patient, severe proteinuria should trigger the suspicion of heavy metal toxicity related to proximal tubular dysfunction. Interestingly, both reports confirm that initial workup for the rheumatological condition is undertaken for this type of patient. If adequate attention is not given, the diagnosis can be delayed for a long time, and the risk of ongoing irreversible exposure will be there.

The mechanism behind the development of osteomalacia remains to be fully elucidated, except for the generalized proximal tubular dysfunction. An interesting observation in our case was persistently low PTH. This reflects elevated FGF-23, which usually suppresses PTH.[1] This can be due to the direct effect of cadmium also as earlier studies have suggested that higher cadmium levels were associated with lower PTH despite elevated calcium excretion[10] However, studies in mice have suggested that cadmium can increase FGF-23 levels along with the decreased activity of SLC34A3 or NPT2C phosphate transporter in the proximal renal tubule.[11] Furthermore, an increase in the GalNAc-T3 activity suppressing the cleavage of the FGF-23 is also implicated in experimental settings.[12] Autopsy studies in cadmium-induced renal phosphate wasting patients suggested a direct impairment of the proximal renal tubular active energy transport. Sparing the distal tubule and glomeruli can lead to urinary phosphate wasting.[13] The finding of enthesopathy in this case cannot be explained thoroughly, and the exact pathogenesis of cadmium-related enthesopathy needs to be understood. However, a multifactorial etiology, including hypophosphatemia and the direct effect of cadmium on enthesis, can be implicated.

From the treatment aspect, considering cadmium's prolonged exposure and long *in vivo* half-life, therapeutic options are limited except for symptomatic therapy. Though evidence is weak, management with chelating therapy like ethylenediaminetetraacetic acid (EDTA) or dimercaprol [British anti-Lewisite (BAL)] can be considered. However, it can further worsen nephropathy,[14,15] mainly when urinary cadmium excretion is very high (more than ten μg/g of creatinine) and was considered for this patient, but the patient was not willing. Nevertheless, it is unlikely that the supportive treatment will alter the natural history of the bone disease.

Conclusion

Here, we describe a case of osteomalacia due to proximal tubular dysfunction in a patient with severe cadmium toxicity caused by occupational exposure to cadmium fumes for a long time. Thus, a careful history and proper diagnostic workup are required for hypophosphatemia patients, and awareness of this rare and

unusual etiology should be kept. Administrative actions should be undertaken to minimize cadmium exposure, and proper social and occupational rehabilitation should be planned considering the morbidity of cadmium exposure. Furthermore, systemic data on disease burden in those working in the silverware industry should be collected.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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