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CASE REPORT

Hypophosphataemic osteomalacia due to cadmium exposure in the silver industry

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Abstract Chronic heavy metal exposure and the health hazards that ensue are important public-health problems. We highlight the occurrence of hypophosphataemic osteomalacia due to chronic cadmium exposure in the silver industry in India. Three silversmiths presented similarly with clinical, biochemical and radiological evidence of hypophosphataemic osteomalacia. Considering their occupation, their blood samples were screened for heavy metals and were found to have toxic levels of cadmium. They were initiated on neutral phosphate and calcitriol. On follow-up, they reported significant reduction in severity of symptoms. It is essential to maintain a high index of suspicion in diagnosing this condition. A thorough knowledge of the occupational background of patients, as well as ambient conditions at the workplace is of utmost importance in contemplating the possibility of such rare occurrences. Moreover, regulatory agencies and policy makers ought to survey the silver industry and ensure that the metals used are within permissible safe limits of exposure.

Key words Cadmium; heavy metals; hypophosphatemic osteomalacia; nickel; silver industry.

Background

Heavy metal contamination is recognized as a serious public-health problem worldwide [1]. Due to their non-biodegradable nature, they may cause many health hazards through industrial exposure, pollutants and exposure to lead containing paint [2]. As previously reported by Sethi *et al.*, silver jewellery manufacturing is an important cottage industry in India [3]. Silver may be mixed with nickel and cadmium in jewellery making. Thus, silversmiths are inevitably exposed to fumes from cadmium and other metals. We describe three unusual cases of cadmium toxicity that caused renal tubular acidosis leading to hypophosphataemic osteomalacia.

Case report

Case 1

A 44-year-old silversmith presented with a 2-year history of worsening bony pains and proximal muscle weakness. At presentation he was ambulant only with support. Other co-morbidities included type 2 diabetes mellitus and hypothyroidism. His past history was significant for renal calculi. Clinical examination revealed diffuse bony tenderness, peripheral neuropathy, bilateral diabetic retinopathy and proximal myopathy. Blood pressure was 100/60 mm Hg. Respiratory system examination was normal.

Investigations showed low serum phosphorus with TmP/GFR (tubular maximum for phosphate reabsorption, corrected for glomerular filtration rate) of 2.1, low uric acid and normal anion gap hyperchloremic metabolic acidosis (Table 1). X-ray of the right forearm (Figure 1a) and both lower limbs showed the presence of multiple pseudo-fractures (Figure 1b). Ultrasound scan of the abdomen revealed bilateral renal calculi. With these biochemical and radiological findings, a diagnosis of hypophosphataemic osteomalacia secondary to renal tubular acidosis was made. His serum calcium, 25-hydroxy vitamin D, parathyroid hormone and FGF23 (Fibroblast Growth Factor 23) levels were within normal limits. His blood glucose levels were uncontrolled with HbA1c of 11.3%. In view of history of chronic exposure to heavy metals, blood was sampled for the same; this showed elevated serum cadmium 33.0 ($N < 5$) mcg/l.

The patient was managed with neutral phosphate, sodium bicarbonate and calcitriol. He was advised to

Key learning points

What is already known about this subject:

- Heavy metal contamination is a public health problem.
- Cadmium is a common heavy metal that is used in the silver industry.
- Chronic exposure to cadmium may cause kidney, bone and cardiovascular diseases.

What this study adds:

- Chronic exposure to cadmium may result in renal tubular dysfunction, which may predispose to osteomalacia.
- A high index of suspicion and a thorough knowledge about the ambient condition that is prevalent at the work place is required to contemplate such rare occurrences.

What impact this may have on practice or policy:

- There ought to be regular monitoring and periodic surveys of these small scale industries, to ensure that the use of these heavy metals is within safe permissible limits of exposure.
- The platform of social media may be utilized widely to disseminate pertinent information regarding safe working practices such as ensuring adequate ventilation especially in an environment where toxic fumes are the major offending agent.

consider an alternate occupation or to abstain from the hazardous exposure to cadmium fumes. On follow-up after 3 months, he reported a 50% reduction in his symptoms; X-ray of the leg showed healing of the pseudo-fractures (Figure 1c). He continues to be on symptomatic treatment. Chelation therapy was not attempted as the patient declined the same and due to the chronicity of the exposure [3].

Case 2

A 40-year-old silversmith presented with a 10-year history of pain in multiple joints and lower limbs. He also had difficulty in rising from a squat. Physical examination revealed lower limb tenderness and proximal muscle weakness. Blood pressure was 110/70 mm Hg. Respiratory, cardiovascular and per abdomen examination were normal.

His blood investigations are shown in Table 1. His inflammatory markers including C-reactive protein and erythrocyte sedimentation rate were not elevated. Autoimmune work up was negative. His biochemical work up was suggestive of a proximal renal tubular acidosis. A heavy metal screen was performed showing elevated cadmium levels (Table 1). His X-ray showed pseudo-fractures in the medial shaft of right and left femur. Like the previous patient, he was asked to abstain from work in order to avoid further exposure. He was treated with neutral phosphate, calcitriol, sodium bicarbonate tablets and syrup potassium chloride. He has been on regular follow-up and reports significant improvement in clinical features with symptomatic treatment.

Case 3

A 43-year-old silversmith working in the same industry as the previous two individuals, presented with history of pain in both hip joints following low intensity trauma, associated with low back ache and difficulty in rising from a squat. On examination, he had tenderness over both hip joints with significant proximal myopathy. Blood pressure was 110/70 mm Hg. Respiratory, cardiovascular and per abdomen examination were normal. Initial investigations are shown in Table 1. He had a minor fracture in the neck of right femur. Heavy metal screening showed elevated cadmium levels (Table 1). With these features, a diagnosis of hypophophataemic osteomalacia secondary to renal tubular acidosis was made. He was managed on the same lines as the previous two patients.

Discussion

Heavy metal poisoning is a public-health problem worldwide. The three cases described above were employed in the silver industry concerned with crafting jewellery. In India, silver jewellery manufacturing is carried out traditionally by the father, his son and other family members at home. Thus, there is no strict enforcement of safety regulations and precautions. The procedure is carried out in a small room about 72 square feet in area, with the silversmiths seated less than one metre from the furnace. The process involves the use of silver, copper, cadmium, nickel and zinc, which are introduced into an iron jar and melted. The exact temperatures involved are not known in this scenario, as the method employed is a crude one and not an automated process. Once the silver solder is prepared, it is moulded into different sized rods and crafted in the shape of various silver ornaments. Although exhaust fans are installed in the place of work, this is probably not sufficient to ensure safe levels of cadmium in the environment surrounding the workers, leading to inhalation of fumes and the adverse effects thereof.

Table 1. Bone mineral parameters and heavy metal screen

Bone mineral metabolism parameters				
Investigation	**Case 1**	**Case 2**	**Case 3**	**Normal range**
Serum calcium (mg/dl)	8.94	9.3	8.40	8.3–10.4
Serum phosphorus (mg/dl)	2.0	2.1	1.9	2.5–4.6
TmP/GFR	2.1	1.6	1.4	2.5–4.5
Serum albumin (g/dl)	4.6	4.8	4.3	3.5–5.0
Creatinine (mg/dl)	0.89	1.43	2.04	0.5–1.4
Uric acid (mg/dl)	1.5	2.2	4.0	4–7
Potassium (m mol/l)	3.9	3.1	3.7	3.5–5.0
Bicarbonate (m mol/l)	20	19	20	22–29
Vitamin D (ng/ml)	33.5	49.5	28.4	30–70
PTH (pg/ml)	89.6	30.9	59.0	8.0–74
ALP (U/l)	586	196	170	40–125
FGF-23 (RU/ml)	43	—	69	21.6–91
Heavy metal screen				
Chromium (mcg/l)	6.0	9.5	12.7	<10
Cobalt (mcg/l)	1.0	1.1	1.4	<4
Arsenic (mcg/l)	13.6	9.4	10.3	<23
Mercury (mcg/l)	<0.5	12.2	12.5	<10
Lead (mcg/dl)	2.3	3.6	3.8	<10
Nickel (mcg/l)	9.5	**33.5**	—	<10
Cadmium (mcg/l)	33.0	>30	>30	<5

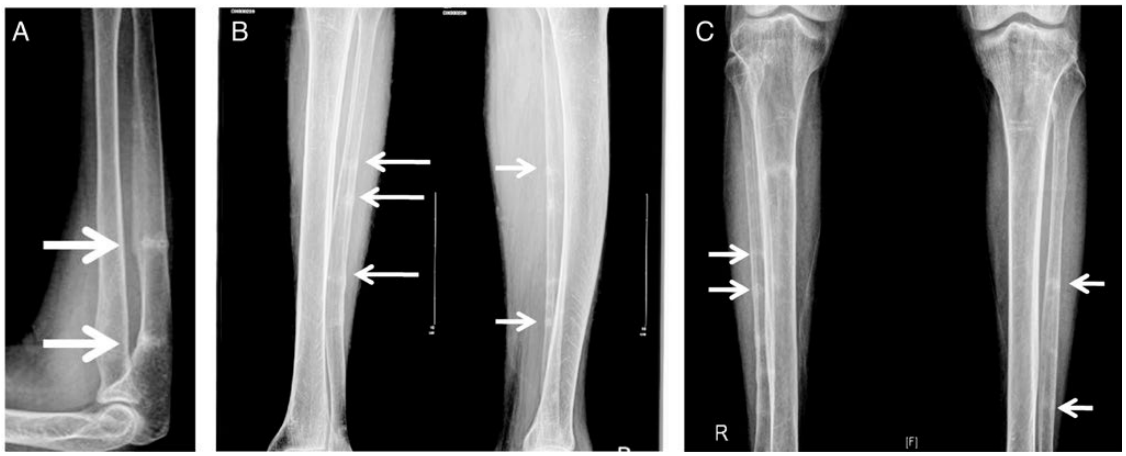

Figure 1. (a) Pseudo-fractures of right forearm, (b) (left panel) multiple pseudo-fractures of lower limb bones and (c) (right panel) healing following treatment.

In this report, all three subjects had features of bony pains, proximal myopathy and pseudo-fractures on radiological evaluation. This presentation is similar to *itai-itai* disease—the renal tubular osteomalacia caused by cadmium exposure, first described in Japan [4]. This occupational health hazard raises several questions about the safety of employees in the silver cottage industry.

Exposure to cadmium is well known to produce kidney, bone and cardiovascular diseases [5,6]. Cadmium is efficiently stored in the kidneys for several years (half-life 10–30 years) and this could cause renal tubular dysfunction, glomerular damage and renal failure. In a population-based study among postmenopausal women, Agneta *et al.* showed a clear association between high body burden of cadmium and low bone mineral density [7]. There are two proposed mechanisms for cadmium induced bone loss; a direct action of cadmium on bone cells and an indirect action on the kidney resulting in excretion of phosphate and calcium. *In vitro* studies have also demonstrated that cadmium can increase the RANKL (Receptor Activator of Nuclear Factor kB – Ligand) expression, TRAP (Tartarate-resistant acid

phosphatase) activity and formation of TRAP-positive cells in the presence of RANKL, resulting in increased osteoclastic activity [8,9]. Cadmium is also known to cause peripheral neuropathy [10]. In this case series however, in subjects 1 and 2, the presence of diabetes may also have contributed to some of the symptoms of peripheral neuropathy.

Nickel enters the body via inhalation, ingestion and dermal absorption. Contact with nickel compounds cause a variety of adverse effects such as contact dermatitis, lung fibrosis, cardiovascular and kidney diseases and cancer of the respiratory tract [11]. Nickel exposure increases the formation of oxygen free radicals, which lead to oxidative damage of the kidney and liver. Nickel in high concentration could result in inhibition of alkaline phosphatase activity, consequently inhibiting bone mineralization [12]. *In vitro* studies in rats suggest that chromium accumulates in femur and causes a decrease in the activity of alkaline phosphatase and TRAP [13]. Other heavy metals known to cause intoxication and various organ manifestations in humans include lead, mercury, arsenic, cobalt and chromium.

Chelation therapy has been attempted in various cases of acute toxicity. Although it was offered to some of these subjects, they were not keen on it. The first step in management of heavy metal poisoning, however, is terminating exposure to the metal. The local medical administrative unit was also intimated of this occurrence such that necessary control measures may be undertaken. They were also encouraged to consider other job opportunities.

Thus, in adults presenting with features of hypophosphatemic osteomalacia, a high index of suspicion is required to consider less common causes for the same. A thorough knowledge of the occupational background of the patient, as well as ambient conditions at the workplace is of utmost importance in contemplating the possibility of such rare occurrences. To the best of our knowledge, this is the first report of a series of patients presenting with hypophosphatemic osteomalacia due to heavy metal toxicity from the silver industry in India. This invokes queries about the safety of workers employed in these small-scale industries. Therefore, regulatory authorities should decide on permissible levels of exposure to these metals to ensure safety of employees and to avert such hazardous insults to health.

Competing interests

None declared.

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