CASE REPORT

Successful treatment of tumour-induced osteomalacia after resection of an oral peripheral ossifying fibroma

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SUMMARY

Tumour-induced osteomalacia is a paraneoplastic syndrome wherein bone is affected by a hormone from a tumour that causes renal phosphate wasting and hypophosphataemia. Here, we present the case of a 31-year-old man who has been suffering from generalised bone pains and a spine deformity that led to loss of height. Pertinent findings are low serum phosphorus, low vitamin D and decreased bone mineral density. These findings led to a diagnosis of osteomalacia. However, the finding of an oral mass raised some questions as to what role it plays in the patient's disease. It was suspected that the oral mass (fibroma) was producing a hormone that led to renal phosphate wasting, hypophosphataemia and then osteomalacia. This hypothesis was proven after surgical removal of the mass led to normalisation of the metabolic derangements and eventually led to a resolution of the bone pains.

BACKGROUND

Tumour-induced osteomalacia (TIO) is a rare paraneoplastic syndrome where in a tumour produces a hormone that leads to renal phosphate wasting and a reduction in 1,25 dihydroxy vitamin D that eventually causes decreased intestinal phosphate absorption. These lead to hypophosphataemia which eventually causes bone pains, bone deformities and distinct radiographic changes in bone.

This case is worth reporting because it adds to our knowledge of metabolic bone disease. Here, we see how bone pains and deformities are due to a seemingly harmless tumour in the patient's mouth.

This case also is an addition to the long list of paraneoplastic syndromes known to affect man.

This patient has been to many doctors for several years and the diagnosis remained elusive for a long time. It is hoped that with this article, we are able to educate other medical professionals so that this entity will not go unnoticed anymore for other patients.

CASE PRESENTATION

A 31-year-old Filipino man consulted for progressive hunchback deformity, marked loss of height and bone pains.

Five years prior to consultation, he started to have low back pain for which he consulted a local physician. He was given pain relievers but pain

persisted. Spine X-rays were performed then which apparently showed normal results. Two years prior to consultation, he started to have bone pains not anymore limited to the back. He is able to walk around the house but would have difficulty walking long distances. He has been to many doctors in their hometown but none were able to provide him with relief from pain. On consultation, his bone pains have become so severe that sitting up from a lying position or even turning in bed would bring him so much pain. He also started to develop kyphosis and that he has become shorter by 14 cm.

He has no previous fracture. He has no other known illnesses. He is not taking glucocorticoids, levothyroxine or anticonvulsants. There is no

Figure 1 An oral mandibular mass just posterior to the right central and lateral anterior incisors.

similar illness in the family. He is a social alcoholic drinker. He is a previous smoker who has stopped smoking several years ago. His work is usually outdoors. He is not a vegetarian. He is married and has three biological children, the youngest being 3 years of age.

He has no constitutional symptoms such as fever, weight loss, anorexia or malaise. He also does not have dyspnoea despite the kyphosis. He mentioned having decreased morning penile erections but continues to shave his facial hair every 2–3 days.

On physical examination, he is awake, coherent and conversant. He is seen initially using a wheelchair. When asked to stand, gross sagittal balance was compensated for by hip extension and partial knee flexion. He had to hyperextend his cervical spine to have parallel vision. He can ambulate with assistance around the room. Vital signs are as follows: heart rate 92/min, respiratory rate 22/min, blood pressure 130/90 mm Hg and temperature 36.8°C. He weighs 55.5 kg. His present height is 161 cm. His known tallest height achieved is 175 cm. He had no neck mass nor goitre. Confrontation testing revealed a normal visual field.

There is a 3×3 cm red fleshy soft tissue mass on the floor of the mouth just posterior to the right lateral mandibular incisor and creating a diastema between the right central and lateral mandibular incisors (figure 1). The mass is not bleeding and had no necrotic areas. When asked, the patient mentioned that this mass has been there for the past 4 years and is not bothering him. He did not initially mention this during the history taking as he thought this had no correlation with his symptoms.

Figure 2 Severe kyphosis with resultant pectus carinatum.

There is thoracic kyphosis and pectus carinatum (figure 2). There is no gynaecomastia and no galactorrhoea. Pulmonary, cardiac and abdominal examinations are normal. There are no gross deformities of the extremities. There are no subcutaneous masses palpated. There is normal-sized external genitalia with bilaterally descended testes, each ~25 g. There is adequate facial, axillary and pubic hair.

INVESTIGATIONS

Spine X-ray showed marked thoracic kyphosis with a Cobb angle of 60° measured from the T2 vertebra to T11 vertebra. There were consequent costal and sternal deformities. There is moderate flattening of the superior thoracic vertebrae (vertebra plana). MRI of the spine also demonstrated exaggerated kyphosis at the thoracic region and also revealed end plate deformities of almost all vertebrae (figure 3).

Work-up for metabolic bone disease revealed serum calcium to be in the range of 2.38–2.65 mmol/L (normal 2.10–2.55), while serum phosphorus was low at a range of 0.28–0.64 mmol/L (normal 0.81–1.49). Serum creatinine was normal at 58.34 µmol/L. Intact parathyroid hormone (PTH) was high at 173.5 pg/mL (normal 10–65). Alkaline phosphatase was elevated at 243 IU/L (normal 38–126). Serum testosterone, luteinising hormone and prolactin were normal.

Initial consideration was primary hyperparathyroidism based on one elevated serum calcium level, consistently low serum phosphorus and elevated intact PTH. Attempts to localise the excess PTH were carried out but neck ultrasound and parathyroid scintigraphy both failed to show enlarged or hyperfunctioning parathyroid glands.

Serum 25-hydroxy vitamin D was low at 13.86 nmol/L (normal >80).

Skeletal survey X-ray showed generalised osteopenia. There were transverse lucencies traversing part of the cortex oriented

Figure 3 MRI of the thoracic spine (sagittal view) showing severe kyphosis.

at right angles to the long axis of the fourth metacarpals, fourth metatarsals and ulnae (figure 4). These are called Looser zones or pseudofractures. There was also endosteal scalloping of the right humerus (figure 5). These X-ray findings are typical of osteomalacia.

Dual emission X-ray absorption bone densitometry showed markedly low z-scores for the lumbar spine (−4.8), right femoral neck (−5.0), left femoral neck (−4.6) and distal 33% of the left forearm (−4.4%).

Measures of renal phosphate wasting were determined.¹ Tubular phosphate reabsorption (TRP) was computed to be 0.8745 using this formula:

$$\text{TRP} = 1 - \frac{\text{serum creatinine} \times \text{urine phosphate}}{\text{urine creatinine} \times \text{serum phosphate}}$$

Tubular maximum reabsorption of phosphate corrected for glomerular filtration rate (TmP/GFR) was low at 0.54 mmol/L (normal for his sex and age: 1.00–1.35). The formula for TmP/GFR is:

$$\text{TmP/GFR} = a \times \text{serum phosphate, where } a = \frac{0.3 \times \text{TRP}}{1 - (0.8 \times \text{TRP})}$$

These results suggest that serum phosphorus is low because of renal phosphate wasting.

DIFFERENTIAL DIAGNOSIS

Since PTH leads to increased phosphate excretion, primary hyperparathyroidism is part of the differential diagnosis. This was in fact the first impression when an elevated serum calcium, low serum phosphorus and high serum PTH were demonstrated. This was eventually ruled out when neck ultrasound and parathyroid scintigraphy did not show any enlarged or hyperfunctioning parathyroids.

Vitamin D deficiency was considered along with the inherited or genetic causes of osteomalacia such as X linked hypophosphataemic rickets, autosomal dominant hypophosphataemic rickets and autosomal recessive hypophosphataemic rickets, but the rapid onset of symptoms and the lack of family history of a similar illness made these unlikely.

Incision biopsy of the oral mass was performed with the expectation that it would be an expansile lytic lesion of bone (also known as a brown tumour) which is seen in primary hyperparathyroidism. Microscopic findings, however, showed a

hypercellular lesion composed of spindly fibroblasts arranged in a whorl-like or storiform pattern. This was assessed to be a peripheral fibroma. Fibromas are a kind of mesenchymal tumour, together with osteomas, chondromas and mixed connective tissue tumours, that may secrete a phosphaturic factor or phosphatonin, now called fibroblast growth factor 23 (FGF23).¹

TREATMENT

To prove that the oral mass is the culprit, phosphorus supplementation and administration of cholecalciferol and calcitriol were intentionally withheld. His dietary intake was also not modified. We wanted to observe if renal phosphate wasting would decrease and if serum phosphorus level would increase with removal of the oral mass being the sole intervention.

Excision of the oral mass was performed. Serum phosphorus immediately increased to 0.66 mmol/L on day 1 postoperative, 0.91 mmol/L on day 2, 1.09 mmol/L on day 3 and 1.06 mmol/L on day 5 (normal 0.81–1.49). From this, it was shown that serum phosphorus normalised 2 days after surgery.

Renal phosphate wasting was also resolved. Renal phosphate reabsorption increased to normal with TPR increasing to 0.933 and TmP/GFR to 1.1699 mmol/L.

Resolution of these metabolic parameters after removal of the oral fibroma with no other intervention proves that the oral fibroma is indeed the cause of the hypophosphataemia and hyperphosphaturia. Demonstration of an elevated FGF23 pre-operatively and resultant decrease postoperatively will confirm that the tumour does produce FGF23 and that this is the culprit hormone. However, measurement of FGF23 could not be performed as the assay is not available in our country.

Microscopic examination of the excised oral mass showed the same hypercellular lesion composed of spindly fibroblasts in a storiform pattern. There were areas in the tumour that showed bone and cartilage as well. Final histological diagnosis is a peripheral ossifying fibroma (figure 6).

The patient was sent home on calcium ascorbate 150 mg +calcium monohydrogen phosphate 500 mg tablet twice daily and cholecalciferol 7000 IU/day orally.

OUTCOME AND FOLLOW-UP

One month after discharge, bone pains have resolved making the patient ambulatory again. He can already move around without any assistance and is already able to ride a motorcycle, simple things that he was not able to do before because of the

Figure 4 Pseudofractures or looser zones on bilateral ulnae, fourth metacarpals and fourth metatarsals.

Figure 5 Endosteal scalloping of the right humerus.

Figure 6 Excision biopsy of the oral mass showing a hypercellular lesion composed of spindly fibroblasts (F) with areas of cartilage (C) and bone (B). Final histopathological diagnosis is peripheral ossifying fibroma. H&E, ×100 magnification.

severe bone pains. The kyphosis remains, however. Repeat serum phosphorus taken 2 months postsurgery is normal at 1.49 mmol/L and 25-hydroxy vitamin D has slightly increased from 13.86 to 20.20 nmol/L.

DISCUSSION

TIO or oncogenic osteomalacia, as seen in this illustrative case, is a paraneoplastic condition where a tumour exerts its effects not via mechanical compression, obstruction or invasion but through alterations in physiology brought about by a chemical substance that the tumour produces. In TIO, this culprit hormone was initially called a phosphatonin and was eventually identified to be FGF23. Complementary DNA clones extracted from a haemangiopericytoma that caused hypophosphataemia and osteomalacia were found to be identical to that of FGF23.²

FGF23, a 251-amino acid 32 kDa protein, acts as a hormone that inhibits the sodium-dependent phosphate co-transporter types 2a and 2c (NaPi-2a and NaPi-2c) located at the proximal tubules of the kidneys. Another biological action is that FGF23 inhibits the renal enzyme 1- α hydroxylase that converts 25-OH vitamin D to its active form 1,25 dihydroxy vitamin D. It also stimulates the enzyme 24-hydroxylase that inactivates 1,25 dihydroxy vitamin D. FGF23 acts on FGF23 receptor types 1, 3 or 4, with α Klotho as its co-receptor without which FGF23 would not be able to exert its effects. These biological actions lead to decreased tubular reabsorption of phosphate, hence excess loss of phosphate through the kidneys. The resultant inhibition of active vitamin D action leads to compensatory hyperparathyroidism.^{3–7}

The characteristic metabolic features are decreased renal tubular reabsorption of phosphate (or increased renal phosphate excretion), low serum phosphate, low 1,25 dihydroxy vitamin D level and elevated FGF23.¹ These metabolic changes contribute to bone pains, bone deformities and increased risk of fractures.

The diagnosis of TIO may take years, averaging 6.7 years, and may take as long as 28 years.⁸ The delay is due to several reasons. First, the bone pains are just dismissed initially since they may not yet be associated with radiographic abnormalities or obvious deformities. Second, serum phosphate is not part of routinely requested laboratory tests. Third, the causative tumour may be small, hidden and clinically silent. Fourth, the disease is rare and not readily recognised.

Mesenchymal tumours, such as haemangiopericytomas, haemangiomas, sarcomas, ossifying fibromas, granulomas, giant cell tumours, osteoblastomas and mixed connective tissue variants, have been found to produce FGF23 in excess and cause osteomalacia.¹

Locating the putative tumour has been straightforward in this case as the mass was large enough to be seen and was in an area that made it readily visible and accessible. In cases where the tumour is small and not readily visible, anatomic (ie, CT scan and MRI) and functional imaging tests (ie, octreotide scan, 18-fluorodeoxyglucose positron emission tomography scan) can be performed to locate them. Venous sampling for FGF23 or measurement of FGF23 in a tumour aspirate can be carried out when a suspect tumour has to be preoperatively proven to secrete this hormone.¹

Definitive treatment for TIO is complete excision of the functioning tumour.⁹ The metabolic parameters are expected to rapidly return to normal as FGF23 has a short half-life of 45 min.¹⁰ Serum phosphate is expected to normalise within 2–10 days.¹

For cases where the putative tumour could not be localised or the patient is not able to undergo or does not consent for surgery, intake of phosphorus supplements and calcitriol is recommended to address the metabolic changes.¹

Patient's perspective

- ▶ My friends have seen me suffer for the past 5 years. The bone pains have made it really difficult for me to do simple things. Walking, standing up from a chair and even turning in bed were very painful.
- ▶ When I came back home to our province after I went to Manila for treatment, my friends and neighbours were amazed at my fast recovery. The bone pains gradually disappeared. They have seen me initially already walking around. Then I would join them play basketball on the street. Then they would already see me ride my motorcycle around town.
- ▶ Thank you to my doctors for being able to recognise that the root cause of all my pains was the mass in my mouth. That mass has been there for a long time but it was not bothering me. It was not painful or bleeding, so I just left it alone. Never did it enter my mind that it was the cause of all my suffering.
- ▶ I am happy that by just simply having that mass removed, the pains in the bones have disappeared. Now I am much relieved! My other wish is that I would eventually regain my height!

Learning points

- ▶ Tumour-induced osteomalacia (TIO) occurs when bone is affected by a tumour that secretes a hormone that causes renal phosphate wasting and impaired production of 1,25 dihydroxy vitamin D leading to decreased intestinal absorption of phosphate. These then lead to chronic hypophosphataemia.
- ▶ Tumours of mesenchymal origin, in this case a peripheral ossifying fibroma, secrete a phosphatonin which has been identified to be fibroblast growth factor 23.
- ▶ Surgical removal of the putative tumour is curative. It leads to rapid normalisation of renal phosphate excretion and serum phosphate levels, and provides relief from bone pains.
- ▶ TIO is a disabling disease. It can be cured if correctly recognised and if the causative tumour is surgically removed.

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Contributors MASS wrote the draft manuscript and was the attending physician of the patient. MASS, MAP, RC and RB took care of the patient with regard to the

medical, endocrine, ENT and orthopaedic concerns. JMC was the pathologist who interpreted the histological specimens. RJG was the radiologist who interpreted the patient's X-ray images. All authors approved the final version of the manuscript.

Competing interests None declared.

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