

Tumour-Induced Osteomalacia in a Patient With Psychiatric, Respiratory, Skeletal and Anaesthetic Challenges

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Abstract

Tumour-induced osteomalacia is a paraneoplastic syndrome characterized by chronic hypophosphataemia due to excessive urinary phosphate excretion caused by fibroblast growth factor-23 secretion by a tumour. In this case report, we present a patient with a 13-year delay in diagnosis, along with other challenges in his management. He had depression and anxiety, which had to be taken into consideration. Likewise, he had chest and spine abnormalities, which made the administration of anaesthesia challenging. Overcoming these challenges allowed successful removal of the tumour, which led to normalization of serum phosphorus, a gradual, progressive increase in muscle strength and joint flexibility, and improvement in mental health status.

Key words: *tumour-induced osteomalacia, oncogenic osteomalacia, phosphorus, hypophosphataemia, metabolic bone disease*

INTRODUCTION

Tumour-induced osteomalacia (TIO) is a paraneoplastic syndrome characterized by chronically low serum phosphorus due to excessive renal phosphate wasting stimulated by tumour-released fibroblast growth factor-23 (FGF-23). Diagnosis is often delayed because bone pain and muscle weakness are attributed to other conditions; because serum phosphorus is not routinely requested; or, even if low phosphorus is detected, the clinicians interpreting the result are unable to correlate the patient's symptoms with the laboratory finding.

In this case report, we present a patient with a 13-year delay in diagnosis, along with other challenges in management. His multiple medical problems necessitated a multidisciplinary approach with the patient at the centre of the decision-making process.

CASE

History

A Filipino male in his 30s presented with difficulty ambulating. Thirteen years prior to consultation, he experienced right ankle pain after participating in a marathon. Ten years prior to consultation, he started to have bilateral lower extremity weakness and difficulty in ambulation. He became kyphotic with a height loss of 13 cm (5 inches). Lower extremity weakness progressed, leading him to become bedbound. He eventually developed pigeon chest deformity, shortness of breath and easy fatigability.

He has had bronchial asthma since childhood, for which he used a budesonide/formoterol 160/4.5 mcg inhaler about once weekly. There was no prior intake of systemic corticosteroids, levothyroxine or anticonvulsants.

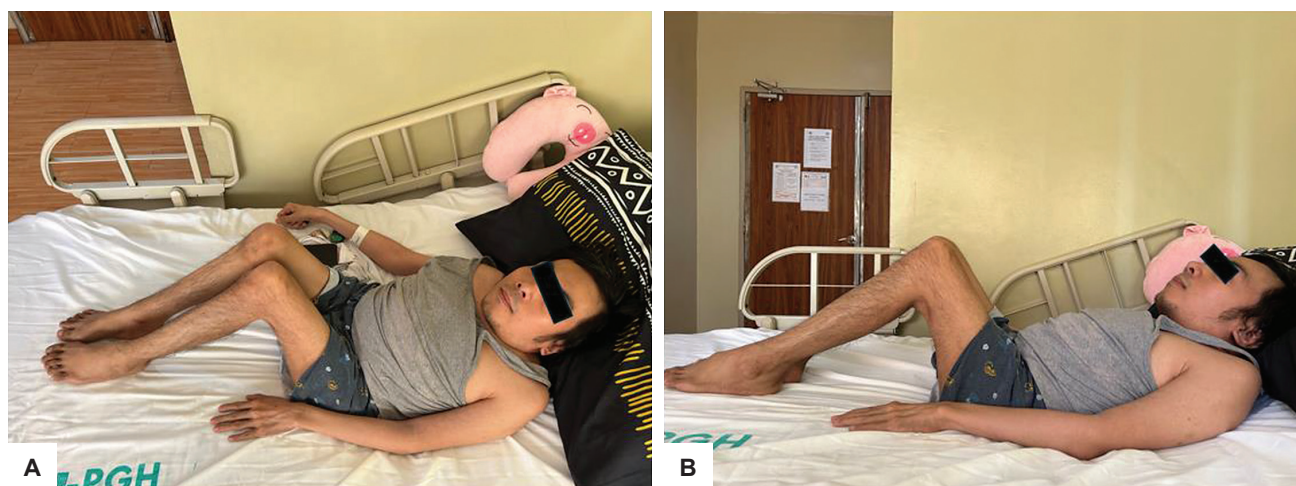


Figure 1. Physical appearance of the patient before surgery, (A) frontal view and (B) lateral view, showing the pigeon chest deformity, contractures of the lower extremities and his bedbound state.

Physical examination

He was awake, coherent and fully conversant. He was bedbound, unable to sit or stand upright. Vital signs were as follows: BP 130/80 mmHg, HR 86/min, RR 18/min, temperature 36.7 °C, oxygen saturation 98% on room air. He had pectus carinatum and bilateral hip and knee flexion contractures, limiting extension. Muscle atrophy was observed in the lower limbs (Figure 1).

Laboratory investigations

He was admitted to a different hospital for leg weakness 10 years prior to this admission. His lab results then showed normal calcium 2.46 mmol/L (9.86 mg/dL), low phosphorus 0.4 mmol/L (1.24 mg/dL) [normal: 0.8-1.6 mmol/L, 2.48-4.96 mg/dL], normal magnesium 0.86 mmol/L (2.09 mg/dL) [normal: 0.7-1.0 mmol/L, 1.70-2.43 mg/dL], low vitamin D 32.75 nmol/L (13.1 ng/mL) [normal: 75-250 nmol/L, 30-100 ng/mL], slightly elevated intact parathyroid hormone (PTH) 8.21 pmol/L (77.42 pg/mL) [normal: 1.06-6.89 pmol/L, 10-65 pg/mL], normal creatinine 61 µmol/L (0.69 mg/dL), increased alkaline phosphatase 449 U/L [normal: 50-136 U/L], normal C-reactive protein <3 mg/L, normal erythrocyte sedimentation rate 9 mm/hr, and normal thyroid function tests. No further tests were done to determine the cause of the low serum phosphorus. In the interim, his weakness progressed and he became bedbound, unable to seek medical consultation again.

Tests done during this admission (March 2024) still showed low serum phosphorus at 0.44 mmol/L (1.36 mg/dL), high intact PTH at 10.71 pmol/L (100.97 pg/mL), and high alkaline phosphatase at 423 U/L. Repeat 25-OH vitamin D was already normal at 91.5 nmol/L (36.60 ng/mL). Total corrected calcium, ionized calcium, creatinine, thyroid function tests, fasting blood sugar, HbA1c, sodium, potassium, magnesium and uric acid were normal.

Low vitamin D status (deficiency and insufficiency combined) is common in the Philippines, with a prevalence of 48.7%.¹ This means that about 1 in every 2 Filipinos would have low vitamin D levels. However, the signs and symptoms that our patient presented with are uncommon. Hence, it is difficult to ascribe his manifestations to vitamin D deficiency. Looking for other causes was warranted. Also, his serum vitamin D had already normalized compared with 10 years earlier, but his signs and symptoms persisted.

To determine renal phosphate wasting, tubular reabsorption of phosphate (TRP) was calculated as 0.8656 using the formula of Payne.²

Maximum tubular reabsorption of phosphate corrected for glomerular filtration rate (TmP/GFR), a measure of renal phosphate wasting, was low at 0.31 mmol/L (reference range for age: 1.00-1.35 mmol/L). This suggests that his kidneys were not adequately reabsorbing phosphorus; hence, phosphorus was excessively excreted in the urine.

FGF-23 assay was not available in the country, so this could not be measured. Serum 1,25-dihydroxyvitamin D assay was likewise unavailable.

X-ray showed generalized osteopenia, chest deformity and old healed fractures at the bilateral 3rd metatarsals. Bone densitometry showed markedly low Z-scores at -6.1, both at the lumbar spine and left ½ radius, suggesting decreased bone mass for age.

Tumours that cause TIO often express the somatostatin receptor SSTR2 on their cell surface. As such, a functional imaging test that uses somatostatin analogues such as octreotide, pentetreotide, DOTATATE, DOTANOC and DOTATOC can locate these tumours. Octreotide scan has a better sensitivity than fluorodeoxyglucose positron emission tomography (FDG-PET) in localizing these tumours.³ Whole-body technetium-99m octreotide scan showed persistent focal tracer accumulation in the distal

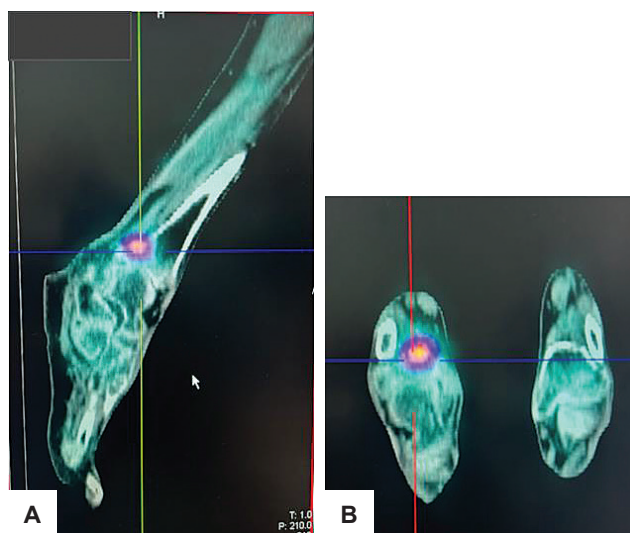


Figure 2. Technetium-99m octreotide scan showing increased focal tracer uptake in the distal right tibia, (A) sagittal view and (B) axial view.

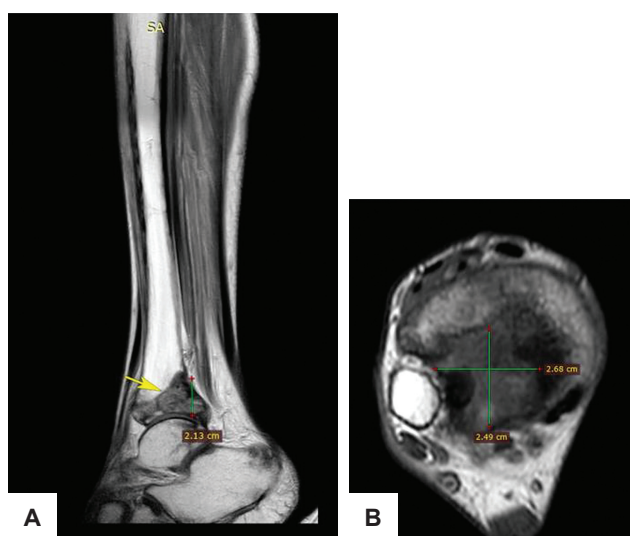


Figure 3. Magnetic resonance imaging showing a mass in the distal right tibia measuring $2.1 \times 2.5 \times 2.7$ cm, (A) sagittal view, with the arrow indicating the lesion, and (B) axial view.

right tibia, pointing to a somatostatin receptor-rich tissue in that area (Figure 2).

In cases of TIO, if functional imaging demonstrates increased uptake of the somatostatin analogue, anatomic imaging is needed to confirm whether that area corresponds to a mass lesion. This is because false-positive uptake of somatostatin analogue may occur in fractures and in areas with inflammation, since lymphocytes also express the somatostatin receptor.³ Magnetic resonance imaging did show a fairly well-defined lesion in the meta-epiphyseal region of the distal right tibia measuring $2.1 \times 2.5 \times 2.7$ cm, the same area where there was increased uptake on the octreotide scan (Figure 3).

DIFFERENTIAL DIAGNOSIS

The common genetic causes of osteomalacia, such as X-linked hypophosphataemia (XLH) and autosomal-dominant hypophosphataemic rickets (ADHR), can easily be ruled out since these are expected to manifest in childhood and adolescence.

Among the acquired causes, vitamin D deficiency, malabsorption and renal wasting disorders were considered. Vitamin D deficiency and malabsorption are characterized by decreased gastrointestinal absorption of phosphorus; hence, the kidneys can conserve phosphorus by reducing its excretion. Since the patient demonstrated decreased tubular phosphate reabsorption, these were unlikely.

A renal wasting disorder seems most plausible in this case, since decreased tubular reabsorption of phosphate was observed, leading to increased urinary phosphate excretion. A common cause of renal phosphate wasting is Fanconi syndrome, wherein there is a defect in the proximal convoluted tubule and failure to reabsorb many molecules such as glucose, phosphate, uric acid, amino acids and bicarbonate. Fanconi syndrome was unlikely since the urinalysis did not show glucosuria or an elevated pH, which are expected in Fanconi syndrome.

FGF-23-mediated renal phosphate wasting was the most likely diagnosis. The findings of hypophosphataemia, increased renal phosphate wasting and somatostatin receptor-rich tumour in the distal tibia strongly suggest the diagnosis of tumour-induced osteomalacia.

MANAGEMENT

The patient's primary clinical problem was progressive difficulty in ambulation due to severe osteomalacia, muscle weakness and prolonged immobility. Management required a multidisciplinary approach involving endocrinology, orthopaedic surgery, rehabilitation medicine, psychiatry, anaesthesia, respiratory medicine and nursing.

Medical management focused on evaluation and monitoring of metabolic abnormalities associated with bone disease, including serial measurements of serum phosphorus, calcium, parathyroid hormone, alkaline phosphatase and indices of renal phosphate handling while the causative tumour was localized. Definitive treatment consisted of surgical excision of the tumour.³

Because the patient had been bedbound for several years with severe muscle atrophy and joint contractures, rehabilitation was initiated to address functional impairment. Under physiatrist supervision, physical therapy included gentle range-of-motion exercises for hip and knee contractures, progressive strengthening of proximal muscles and bed mobility training, with careful progression due to skeletal fragility. Nursing care supported activities of daily living and pressure injury prevention. Psychiatric

support was provided to address anxiety and adjustment difficulties related to chronic illness and planned surgery. Respiratory status was closely monitored because chest wall deformity had resulted in restrictive lung disease with implications for perioperative management.

PSYCHIATRIC CHALLENGE

The patient found it emotionally difficult to accept his transition from an active individual to a severely ill, bedbound state. This abrupt change caused episodes of depression and anxiety, manifesting as crying spells, low mood, anergia, rumination over past losses and apprehension about the future. Although surgery was the recommended next step, he requested temporary discharge and readmission after one month to prepare himself emotionally.

On screening, he scored 16 on the Patient Health Questionnaire-9 (PHQ-9), indicating moderately severe depression, and 19 on the Generalized Anxiety Disorder-7 (GAD-7) scale, indicating severe anxiety. Psychotherapeutic interventions were delivered by a psychiatrist during daily in-hospital rounds, providing space for him to share his narrative, grieve his losses and develop healthy coping strategies. To address his anxiety, the medical team carefully and repeatedly explained the diagnostic and surgical plans. Alprazolam was used sparingly for severe panic attacks, with greater reliance on cognitive, behavioural and mindfulness techniques. Education and support were also extended to his mother, the primary caregiver, to mitigate potential caregiver burnout.

RESPIRATORY CHALLENGE

Osteomalacia had led to pectus carinatum and rib deformities. Because of these, he had severe restrictive lung disease and was at risk for respiratory failure if sedated. Preoperative arterial blood gas showed compensated respiratory acidosis with pH 7.38, pCO₂ 48 mmHg, pO₂ 74 mmHg, HCO₃ 27.3 mEq/L, O₂ sat 95% on room air. Sedation was intentionally avoided to prevent worsening of respiratory acidosis.

SKELETAL CHALLENGE

Severe osteomalacia had resulted in skeletal deformities, including cervical deformity, thoracolumbar kyphosis and fixed flexion contractures of the hips and knees, which significantly limited positioning during the surgical procedure. These skeletal abnormalities also increased the risk of fractures during patient transfer and intraoperative manipulation. Because of the spinal deformity and inability to assume the sitting or lateral position required for neuraxial techniques, spinal anaesthesia was considered technically difficult. Careful handling and positioning precautions were therefore implemented during perioperative care to minimize the risk of skeletal injury. In addition, rehabilitation interventions were initiated

to address musculoskeletal impairment, including gradual range-of-motion exercises for contractures and progressive muscle strengthening under the supervision of a physiatrist.

CONDUCT OF ANAESTHESIA

Anaesthesia was required to facilitate the surgical procedure that involved painful manipulation of bone while also addressing the patient's anxiety disorder. Management was challenging due to cervical deformity, fixed contractures limiting positioning and severe restrictive lung disease from the thoracolumbar kyphosis. Neuraxial anaesthesia was considered technically difficult because of spinal deformity and positioning limitations, with anatomical variations potentially leading to unpredictable local anaesthetic spread.^{4,5} General anaesthesia was also considered high risk due to anticipated airway difficulty and severe restrictive lung disease predisposing to perioperative respiratory complications.⁶ A peripheral nerve block approach with light dexmedetomidine sedation was therefore selected to provide adequate surgical anaesthesia while maintaining airway patency and cardiorespiratory stability.^{7,8}

SURGICAL MANAGEMENT

A corticotomy was made, and curettage was undertaken of the firm tan lesion in the posterolateral corner of the tibial plafond. Morselized bone allograft was used to pack the cavity and reconstruct the corticotomy opening. Post-operatively, the distal right leg and ankle were protected with a temporary splint. The surgery was completed, and the patient remained comfortable and pain-free.

HISTOLOGIC ANALYSIS

Histopathologic examination of the tumour showed a predominantly fibro-osseous lesion composed of bland spindle cells with moderate pink cytoplasm and ovoid to spindled nuclei. There was woven bone formation and deposits of haemosiderin (Figure 4A and 4B). Grungy calcifications, necrosis, severe pleomorphism and increased mitotic activity were absent.

Immunohistochemistry (IHC) (Figure 4C to 4F) showed strong diffuse nuclear staining for SATB2, which is suggestive of osteoblastic differentiation. SSTR2A showed weak to moderate, focal positivity in the spindle cells. ERG showed very focal staining as well. SMA and CD56 also showed some positivity. The following were negative: desmin, h-caldesmon, CD68, CD34, and H3.3 G34W (a marker for giant cell tumour of bone). Given the immunohistochemical findings, a phosphaturic mesenchymal tumour (PMT) should be considered. However, the tumour lacked some of the usual histologic features for PMT, and so molecular testing for *FN1* translocation was recommended. Unfortunately, this could not be done because the test is unavailable in our country.

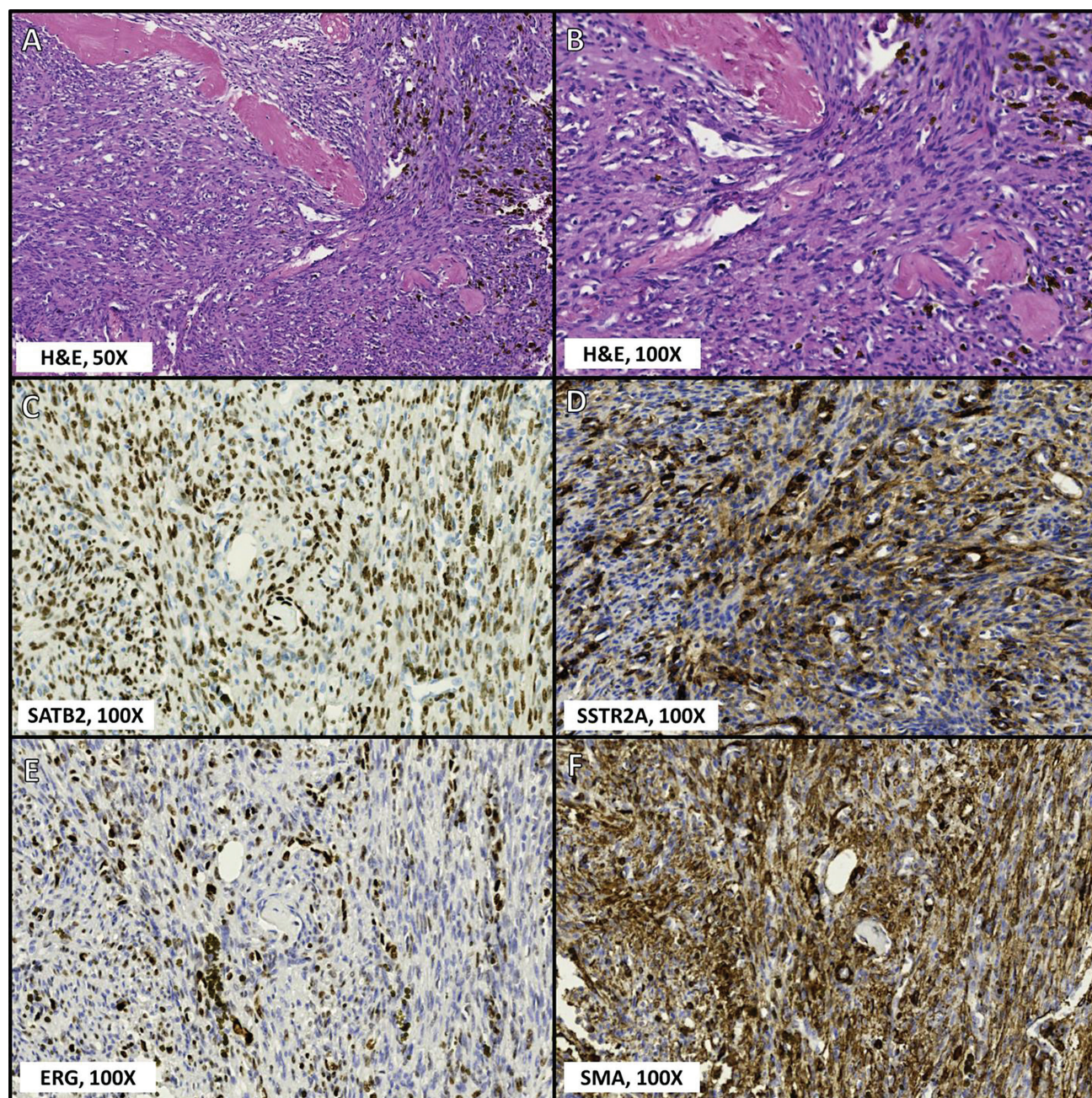


Figure 4. Histopathologic examination showing a predominantly fibro-osseous lesion composed of bland spindle cells with moderate pink cytoplasm and ovoid to spindled nuclei, with woven bone formation and deposits of haemosiderin (A, H&E, 50 $\times$; B, H&E, 100 $\times$). Immunohistochemistry was positive for SATB2 (C), SSTR2A (D), ERG (E) and SMA (F) (100 $\times$).

OUTCOME AND FOLLOW-UP

Even without phosphorus or vitamin D supplementation, serum phosphorus increased to a normal level (0.82 mmol/L) by the 5th postoperative day and remained within the normal range thereafter (Figure 5).

TmP/GFR on the 5th postoperative day increased from 0.31 to 0.77 mmol/L. Five months postoperatively, his serum phosphorus was 1.42 mmol/L, while TmP/GFR was elevated at 1.66 mmol/L, suggesting high tubular reabsorption of phosphate.

Two years after surgery, having been previously bedbound, he can already lift his torso and assume a semi-sitting position. His muscle strength has increased: having previously had difficulty raising his arms even to comb his hair, he can now lift a 2-kg dumbbell in each hand. His leg muscles have visibly increased in bulk (Figure 6). Our patient continues to receive physical therapy at home. Surgical release of contractures is planned to improve joint mobility.

Emotionally, his depressive symptoms have improved, with his PHQ-9 score decreasing from 16 (moderately severe) to 2 (minimal or none). His anxiety has likewise

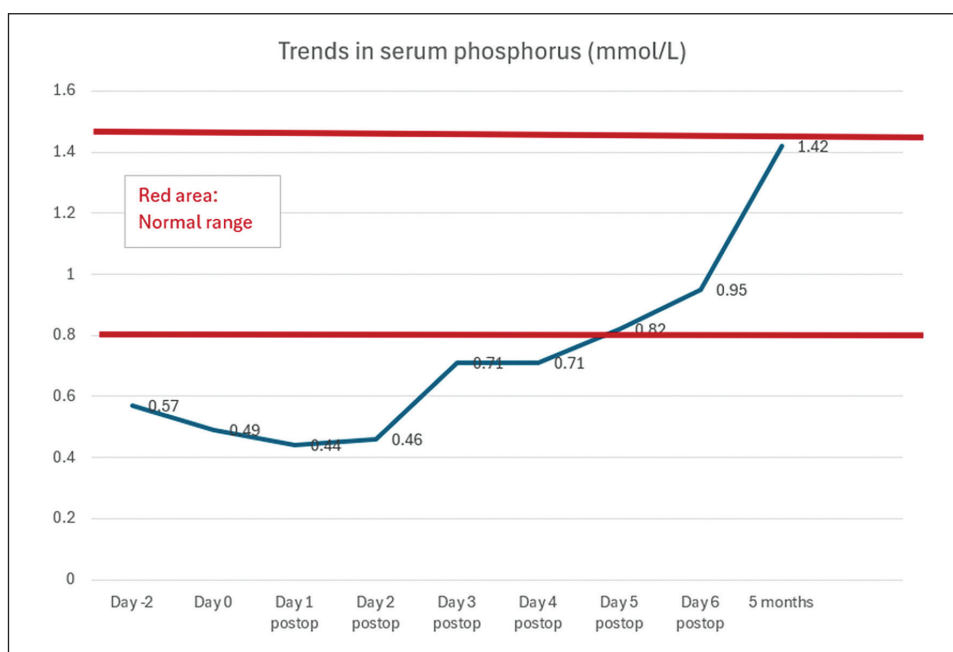


Figure 5. Trends in serum phosphorus levels before and after curettage.



Figure 6. On follow-up two years after surgery, (A) the patient can now assume a semi-sitting position and (B) can lift a 2-kg dumbbell (on each arm). Compared with Figure 1, his leg muscles have increased in bulk.

improved, with his GAD-7 score decreasing from 19 (severe anxiety) to 3 (minimal anxiety). His mental health symptoms improved even without the use of psychotropic medications at home.

DISCUSSION

Our patient experienced bouts of depression and anxiety related to his adjustment from being independent to being bedbound. Ni et al reported a patient with TIO who also had profound depression. That patient became more independent in activities of daily living by 10 months after surgery and had not experienced severe depression since.

His quality of life and social functioning had markedly improved.⁹ Although our patient is not yet able to sit, stand or walk, his symptoms of depression and anxiety have already improved with the recovery of his muscle strength.

DeCorte et al showed that depression and anxiety occurred in 11% of patients with TIO.¹⁰ Also, patients with chronic idiopathic hypophosphataemia had higher rates of depression than those who had normal phosphorus levels.¹¹

Verma et al and Pandey et al separately reported patients with respiratory muscle weakness in whom the possibility

of postoperative ventilatory support was discussed, similar to our patient. Nevertheless, their patients tolerated inhalational anaesthesia with sevoflurane and isoflurane and were successfully extubated afterward.^{12,13}

LEARNING POINTS

- Low serum phosphorus is an often-overlooked cause of metabolic bone disease. This must not be disregarded but must be recognized and addressed to prevent the debilitating effects of osteomalacia.
- The combination of low serum phosphorus, osteomalacia and renal phosphate wasting in adulthood – even in the presence of low vitamin D – should prompt a search for a causative tumour using functional and anatomical imaging tests.
- Treatment of tumour-induced osteomalacia involves surgical removal of the causative tumour, which leads to prompt resolution of hypophosphataemia.
- In this patient, osteomalacia led to chest deformity, spinal deformity and contractures that made inhalational and neuraxial anaesthesia inappropriate. Eventually, peripheral nerve blocks involving the sciatic, femoral and lateral femoral cutaneous nerves afforded loss of sensation to painful stimuli and facilitated successful surgery.
- Patients with chronic debilitating illnesses are predisposed to depression and anxiety that need to be considered in the planning of the timing of surgery. Respect for patient autonomy and consideration of their mental readiness should be observed.

PATIENT PERSPECTIVE

"I felt depressed because I was stuck at home in the Philippines. It seemed like I was a prisoner in my own room and couldn't do anything myself. Until one day, I decided to face my demons again and fight my anxiety and depression. I opted to consult again and met my orthopaedic surgeon and endocrinologist. My doctors worked very hard to investigate the main problem which has been causing weakness in my bones and muscle for more than a decade. It gave my hopes back high again and saw that everything is heading back to normal. We were able to go through surgery. Thanks to my team of doctors."

"I can now feel many changes in my body. For normal people, these might be very trivial but for me, it is only now that I'm able to experience these changes. I can now lift up my feet and legs, and able to do sit-ups without the help of my hands. I can now lift my body from the bed since my back muscles and hips have started to regain power. The grip in my hands is getting stronger, too. I can now open jars and press spray bottles, things which I was not able to do before. The muscles in my chest, arms and hips have started to bulk up now, too."

Ethical Consideration

A signed patient consent form was obtained before manuscript submission.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

CRedit Author Statement

MASS: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft preparation, Visualization, Supervision; **PLOC:** Formal analysis, Investigation, Writing – review and editing; **DJECL:** Formal analysis, Investigation, Writing – review and editing, Visualization; **EGO:** Formal analysis, Investigation, Writing – review and editing, Visualization; **JSEQ:** Formal analysis, Investigation, Writing – review and editing; **JEHA:** Formal analysis, Investigation, Writing – review and editing; **ABA:** Formal analysis, Investigation, Writing – review and editing; **EHW:** Conceptualization, Formal analysis, Investigation, Writing – review and editing, Supervision.

Data Availability Statement

No datasets were generated or analyzed for this study.

Author Disclosure

The authors declared no conflict of interest.

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None.

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