

Perioperative management of patients with severe hypophosphataemia secondary to oncogenic osteomalacia: Our experience and review of literature

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ABSTRACT

Oncogenic osteomalacia (OOM) is a rare paraneoplastic syndrome associated with mesenchymal tumours. It is characterised by phosphaturia, hypophosphataemia, decreased serum Vitamin D3 levels and severe osteomalacia. OOM-inducing tumours are usually benign, arising either from bone or soft tissue, with extremities and craniofacial region being the most common sites. Surgical resection of the tumour remains the mainstay of treatment. Challenges to an anaesthesiologist arise when such patients are planned for surgical resection of the underlying tumour. All the perioperative dilemmas are directly related to the severe hypophosphataemia. We describe three such cases of OOM and their perioperative management.

Key words: Oncogenic osteomalacia, hypophosphataemia, tumour-induced osteomalacia

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INTRODUCTION

Oncogenic osteomalacia (OOM) is a rare paraneoplastic syndrome associated with mesenchymal tumours. It causes phosphaturia, hypophosphataemia and decreased Vitamin D3 levels resulting in osteomalacia. It is a disorder with a complex diagnostic approach such that by the time the syndrome is diagnosed, patients may develop severe osteoporotic changes and often extreme debilitation. Surgical removal of the primary tumour is the definitive treatment for OOM. We have described the perioperative concerns and management of three such patients undergoing resection of the primary tumour, two under general anaesthesia (GA) and one under subarachnoid block (SAB).

CASE REPORT

Patient 1

A 45-year-old male was suffering from diffuse bilateral lower limb pain for the past 8 years and experiencing bilateral lower limb weakness for the past 1 year. He also complained of recent onset anterior chest pain on coughing. Misdiagnosed as an autoimmune

disorder, he had received treatment in the form of oral corticosteroids for a period of 4 months with no clinical benefit. He was finally diagnosed as a case of OOM with the primary tumour being a left mandibular soft tissue tumour and was planned for segmental resection of the left mandible under GA.

Patient 2

A 65-year-old male was suffering from diffuse bilateral lower limb pain for the past 15 years and bilateral lower limb weakness for the past 8 months. He had taken oral calcium and Vitamin D supplements for 6 months with minimal clinical improvement. He was diagnosed to have OOM with the primary tumour being a mastoid mesenchymal tumour. This

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patient was planned for left temporal craniotomy and mastoidectomy under GA.

Patient 3

The patient in this case was a 27-year-old male suffering from generalised body ache for the past 7 years and gradually progressive proximal muscle weakness of the upper and lower limbs for the past 2 years. For the past 2 years, he was bedridden due to severe pain. Weakness of the bones had led to convex deformities of the left upper arm and pectus excavatum. A delayed diagnosis of OOM was made secondary to a left gluteal soft tissue tumour; resection of the tumour was planned under SAB.

The biochemical, radiographic and histopathological investigations of these patients are described in Table 1. We report our experience of administering anaesthesia to these three patients with OOM after obtaining written informed consent from each patient.

All the patients had proximal myopathy of bilateral lower limbs. Patient 1 and patient 3 also had respiratory muscle weakness manifested by poor cough and a decreased breath-holding time of 18 and 14 s, respectively. There was no cardiovascular or neurological involvement in any patient. The

possibility of post-operative ventilator support was explained to the patients and consent was taken.

In the pre-operative period, all the three patients had moderate hypophosphataemia (1.0–1.5 mg/dl) and were managed with oral phosphate supplementation in the form of Na_2HPO_4 and NaH_2PO_4 of 4.6 g and 1.3 g, respectively, at a dose of 3 g/day for 2 weeks.^[1] However, this did not lead to significant improvement in serum phosphate levels [Table 1].

Patient 1 and patient 2 underwent surgery under GA. For patient 1, following premedication with intravenous midazolam 1 mg and fentanyl 150 μg , anaesthesia was induced using 100 mg propofol, and endotracheal intubation was facilitated by administering vecuronium 8 mg intravenously. Thereafter, anaesthesia was maintained with sevoflurane 2.5% in $\text{O}_2/\text{N}_2\text{O}$ (50:50) (minimum alveolar concentration: 1–1.2) and intermittent fentanyl boluses. Due to nonavailability of a neuromuscular monitor, we decided not to repeat muscle relaxant intraoperatively. Special attention was paid to careful positioning and adequate padding of bony points. Intraoperatively, 15 Mmol potassium phosphate was supplemented intravenously as an infusion over 4 h. At the end of the surgery, residual neuromuscular block was reversed with neostigmine and glycopyrrolate, and trachea

Table 1: Biochemical, radiographic and histopathological investigations of patients 1, 2 and 3

Biochemical investigations	Patient 1	Patient 2	Patient 3
Serum calcium	Normal	Normal	Normal
PO_4 (2.5-4.5 mg/dl)	Low (1.5 mg/dl)	Low (1.5 mg/dl)	Low (1.0 mg/dl)
PTH (10-55 pg/dl)	77.3 (mildly raised)	Normal	Normal
Vitamin D3	Normal	Normal	Normal
ALP (110-350 IU/L)	259 IU/L (normal)	866 IU/L (highly elevated)	7096 IU/L (highly elevated)
FGF-23 (0-150 RU/ml)	1104 RU/ml	153.5 RU/ml	7397.5 RU/ml
Bone scan	Osteopenic lumbar spine and long bones	-	-
Skeletal survey	Multiple fractures (including ribs)	Multiple fractures	Multiple fractures (bilateral scapulae, multiple ribs and vertebrae, pubic rami, fibula, metatarsal and bilateral radii)
Ga68-DOTANOC PET-CT scan	Somatostatin receptor expressing soft tissue density lesion in proximity to the left ramus of the mandible	Somatostatin receptor expressing soft tissue density lesion in mastoid part left temporal bone	Somatostatin receptor expressing soft tissue density lesion in subcutaneous fat adjoining the left hip joint
Histopathology	Phosphaturic mesenchymal tumour	Phosphaturic mesenchymal tumour	Phosphaturic mesenchymal tumour
Diagnosis (causative lesion)	Mandibular tumour	Mastoid tumour	Left hip soft tissue tumour
Serial serum phosphate values (mg/dl)	Patient 1	Patient 2	Patient 3
On admission	1.5	1.5	1.0
Immediate pre-operative (after oral phosphate supplementation \times 2 weeks)	2.0	2.4	2.5
Immediate post-operative	2.4	2.8	3.2
After 2 weeks	3.4	4.8	4.5

PTH – Parathyroid hormone; ALP – Alkaline phosphatase; FGF-23 – Fibroblast growth factor-23; PET – Positron emission tomography; CT – Computed tomography

was extubated after ensuring complete recovery. The patient was conscious, pain-free and normothermic and was monitored overnight in the post-anaesthesia care unit (PACU).

For patient 2, anaesthesia was conducted in a manner similar as described for patient 1. However, intraoperative neuromuscular monitoring was performed to guide the use of muscle relaxant, and trachea was extubated only when the train-of-four ratio was more than 0.9. The surgery proceeded uneventfully.

For patient 3, SAB was administered by paramedian approach at L3–L4 level using a 25-gauge Quincke Babcock needle with the patient in right lateral position. A volume of 2.2 millilitres of 0.5% hyperbaric bupivacaine with 25 µg fentanyl was given, and adequate block was achieved bilaterally up to T10 level. The surgical resection of the tumour was then performed. No phosphate supplementation was administered intraoperatively. The patient remained haemodynamically stable and was shifted to the PACU for observation. In the PACU, adequate analgesia was provided, prevention of deep venous thrombosis ensured and close monitoring for hypo- and hyper-calcaemia was done.

Serial monitoring of phosphate levels demonstrated a significant clinical and biochemical improvement over the next 2 weeks in all the three patients [Table 1].

DISCUSSION

OOM is a rare paraneoplastic syndrome associated with mesenchymal tumours. It is characterised by phosphaturia, hypophosphataemia, decreased serum Vitamin D3 levels and osteomalacia. The OOM-inducing tumours are usually benign, arising either from bone or soft tissue, with extremities and craniofacial region being the most common sites, as in two of patients, one with a mandibular tumour and the other with a left gluteal tumour. Phosphaturic mesenchymal tumour of the mixed connective tissue type is the most common subtype. It secretes phosphaturic hormones, among which fibroblast growth factor (FGF)-23 is the main one.^[2] FGF-23 reduces renal phosphate absorption by suppressing the expression of sodium phosphate cotransporter in the brush border membrane of proximal tubules. It also reduces intestinal phosphate absorption by decreasing the production of 1,25 hydroxyvitamin D in the kidneys,

which mediates intestinal absorption of phosphate. Simultaneously, FGF-23 inhibits the compensatory mechanism of increased calcitriol levels. Calcium and phosphorus homeostasis is thus perturbed, leading to severe hypophosphataemia.^[3] FGF-23 has also been implicated as a cause of hypophosphataemia in genetically mediated rickets and osteomalacia.^[4]

The mean age at onset of symptoms is 40 years and occurs in both sexes. Clinically, OOM is characterised by slowly progressive musculoskeletal pain, muscle weakness, fatigue and skeletal abnormalities, including recurring long-bone and vertebral fractures in some cases. Associated biochemical abnormalities are highly characteristic including hypophosphataemia, phosphaturia and inappropriately low circulating concentrations of serum 1,25-dihydroxyvitamin D.^[5] However, in all the three patients, serum Vitamin D3 levels were found to be normal.

As it is well known, phosphorus is a critical element of the body and is needed for multiple physiological functions. Its deficiency, needless to say, precipitates various systemic problems [Table 2].^[6]

The diagnosis of OOM is relevant therapeutically because resection of the implicated tumour is said to

Table 2: Clinical implications of hypophosphataemia

System	Implications	Assessment/test
Musculoskeletal	Osteomalacia Pathological fractures Chronic myopathy Rhabdomyolysis	X-ray
Cardiovascular	Left ventricular dysfunction Arrhythmias Impaired response to vasopressors	Electrocardiogram/ Echocardiography
Respiratory	Rib/vertebrae fracture Chest wall deformity Decreased diaphragmatic contractility Failure to wean from ventilatory support	Pulmonary function test
Central nervous system	Central/peripheral neuropathy Central pontine myelinolysis Seizure, coma Neuropathy mimicking GBS	Electroencephalogram
Metabolic	Reduced sensitivity to insulin	Blood sugar levels
Haematological	Haemolytic anaemia Reduced chemotaxis and antibacterial activity	Complete blood count

GBS – Guillain–Barré syndrome

be the definitive cure for this condition. If the tumour cannot be localised or is not surgically resectable, medical therapy with phosphate supplementation and calcitriol or alphacalcidol may be tried, although with limited benefit. Octreotide therapy has also been suggested to improve the phosphate wasting.^[7]

Challenges to an anaesthesiologist arise when such patients are planned for surgical resection of the tumour. All the perioperative dilemmas are directly related to the severe hypophosphataemia. Preoperatively, oral phosphate supplementation in the form of $\text{NaH}_2\text{PO}_4 + \text{Na}_2\text{HPO}_4$ 3 g/day needs to be given to these patients. However, they do not respond much to medical management and invariably have to be taken up of surgery with suboptimal serum phosphorus levels.

In most patients, like in ours, the musculoskeletal signs and symptoms precede the diagnosis of the underlying tumour by months to years. By this time, osteomalacia is well advanced, and underlying myopathy maybe aggravated due to possible use of long-term oral steroid intake prescribed to the patients on previous erroneous diagnosis of autoimmune disease as in our first patient. Positioning in these patients needs to be done very carefully, ensuring adequate padding at pressure points. The patient must be handled gently due to risk of pathological fractures.^[8] We had to practice utmost care while positioning our patients, especially patient 3 for the SAB as he had excruciating pain and extremely fragile bones.

Alkalosis and hyperglycaemia can worsen the already existent hypophosphataemia by stimulating movement of phosphorus into the cells. Hyperventilation and dextrose-containing fluids must thus be avoided.

Hypophosphataemia impairs the contractility of diaphragm and may lead to delayed weaning from mechanical ventilation. Cardiovascular complications including severe arrhythmias and even cardiac failure have been reported due to hypophosphataemia; hence intravenous phosphorus supplementation was done intraoperatively in two of our patients, though we did not find any literature commenting upon the utility of the same. We closely monitored the haemodynamics and phosphate levels of the patients intraoperatively as well as postoperatively for the next 24 h.^[9]

As expected, all the three patients demonstrated a significant clinical and biochemical improvement following the resection of the implicated tumour and were discharged uneventfully with near normal serum phosphate levels at the end of 2 weeks.

CONCLUSION

OOM is a rare paraneoplastic syndrome. It may precipitate severe hypophosphataemia if diagnosis is delayed, leading to a number of complications and perioperative challenges. With the advent of novel technology, an earlier diagnosis, therapeutic surgical management and vigilant adherence to the pertinent perioperative concerns related to severe hypophosphataemia are crucial for favourable outcome in these patients.

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Conflicts of interest

There are no conflicts of interest.

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