CASE REPORT

Severe, reversible dysphagia and malnutrition in a patient with tumour-induced hypophosphataemia

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SUMMARY

Up to 20% of hospitalised patients may have low serum phosphate concentrations. In certain groups, such as patients with chronic alcohol overconsumption, severe trauma or sepsis, the prevalence may be 30%–50%. Profound hypophosphataemia is less common, but may lead to severe physiological disturbances. In rare cases, hypophosphataemia is caused by phosphaturic substances excreted from a tumour. Osteomalacia with chronic bone pain and fractures, as well as muscle weakness, is common in such patients. The tumours are often small and difficult to detect. Studies suggest that fibroblast growth factor 23 is a reliable marker for detection of these tumours. Persistent hypophosphatemia unresponsive to supplements should raise clinical alertness. With complete resection of the neoplasm, the symptoms rapidly reverse. If the tumour cannot be removed, treatment relies on supplementation with phosphate and active vitamin D compounds. We present a case report of a patient with severe hypophosphataemia, osteomalacia, dysphagia and malnutrition.

BACKGROUND

Hypophosphataemia may be caused by impaired intestinal uptake (malabsorption), increased urinary excretion (renal wasting) or altered distribution of phosphate between intracellular and extracellular compartments (refeeding syndrome).¹ Muscular weakness, bone pain and altered mental status are the most common presenting symptoms in severe hypophosphataemia, and the condition may be associated with hypoxia, tachycardia, cardiac failure and general cell membrane rigidity. Healthy adults are in phosphate balance, that is, dietary intake has little effect on phosphate homeostasis because of rapid renal adaptation. However, tubular reabsorption of phosphate may be affected by substances secreted by certain tumour cells. These substances can lead to a major renal loss of phosphate with severe repercussions. Prior studies advise that tumour-induced osteomalacia should be suspected in patients presenting with suggestive symptoms, most commonly bone pain, muscle weakness, multiple fractures and persistent hypophosphataemia.^{2–4} Dysphagia and malnutrition are not yet described as such symptoms. The aim of this case report is to illustrate how even these non-specific symptoms should lead to further investigation. Hopefully, this case report can raise awareness of tumour-induced hypophosphataemia, especially since early diagnosis and treatment are essential to avoid major morbidity and a fatal outcome.

CASE PRESENTATION

A 76-year-old man was hospitalised in February 2017 with nausea, respiratory pain, severe dysphagia, hiccups, emesis and major difficulties eating and drinking. He had an unintended weight loss of 17 kg over the last 9 months and suffered from general muscle weakness and severe malnutrition. The patient had been diagnosed with a paraganglioma in December 2012. The tumour was located in posterior cranial fossa expanding into the cerebellum and cervical vertebra C1. Surgical removal had been refused by neurosurgeons due to both coronary heart disease and the inaccessible localisation of the tumour. The patient was therefore treated with radiotherapy, 60 Gy by intensity-modulated radiation therapy. The patient had also been diagnosed with osteoporosis at the orthopaedic department in October 2012. At that time, his general practitioner (GP) had assessed blood samples showing low phosphate levels (0.5 mmol/L; normal range 0.8–1.4 mmol/L), normal serum calcium levels (2.15 mmol/L; normal range 2.15–2.51 mmol/L) and elevated alkaline phosphatase levels (182 U/L; normal levels <105 U/L). A DXA scan confirmed osteoporosis, and from January 2013, the patient was given bisphosphonate 70 mg once a week. During the period from 2012 to 2017, the patient was admitted to several rehabilitation units because of general muscle weakness and frailty, skeletal pain and weight loss. He also experienced several spontaneous fractures of the hip, several vertebrae and costae, clavicle and talus.

INVESTIGATIONS

The patient attributed his weight loss to severe dysphagia. A gastroscopy was therefore performed, showing no signs of obstruction. However, a radiological contrast examination of the upper GI tract showed signs of severe dysmotility, especially in the oesophagus, which was nearly in a paralytic state. A contrast CT scan of the thorax, abdomen and pelvis did not show any sign of malignancy.

Biochemically, a very low serum phosphate level of 0.1 mmol/L was discovered at the time of hospitalisation. Despite administering large amounts of phosphate, both orally and parenterally, it was difficult during the first 7 days to elevate serum phosphate levels above 0.5 mmol/L. His medication with bisphosphonate was discontinued on day 4 after admission. However, from the blood tests performed by his GP, we knew that the patient already had hypophosphataemia before he started using bisphosphonates in 2013.

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Table 1 Blood and urinary levels of phosphate during phosphate supplementation

	Day 1 (admission)	Day 3	Day 5	Day 8	Day 15	Day 16 (discharge)	1 month postdischarge	1 year postdischarge
Serum phosphate level (mmol/L)	0.1	0.3	0.3	0.4	0.6	0.6	0.6	0.8
Phosphate supplements (mmol/day)	68	88	106	136	96	96	96	64
Urinary phosphate level (mmol/L)	NA	32	NA	49	NA	NA	NA	NA

NA, not available.

Urine was collected for 24 hours starting on day 8, and urine phosphate levels were measured at 49 mmol/L, which is unusually high. By giving 40 mmol phosphate intravenously and 3 g phosphate orally (ie, 136 mmol in total) daily for 5 days, the patient's serum phosphate levels slowly started to increase. Two days before discharge (day 15 after admission), we discontinued intravenous substitution. The patient then maintained stable phosphate levels at 0.6 mmol/L with 3 g of oral phosphate daily (summarised in [table 1](#)).

At admission, he had an albumin level of 29 g/L, albumin-adjusted serum calcium level of 2.08 mmol/L, serum iron level of 4 µmol/L and serum folic acid level of 24.1 nmol/L. Serological tests for coeliac disease were negative. Blood samples showed a normal 25-hydroxy-vitamin D level of 57 nmol/L and a normal vitamin B12 level of 376 pmol/L. Blood analysis showed an elevated fibroblast growth factor 23 (FGF-23) level of 920 ng/L (normal range <49 ng/L).

DIFFERENTIAL DIAGNOSIS

FGF-23-mediated hypophosphataemia with increased renal excretion could be hereditary (eg, X linked autosomal hypophosphataemia or autosomal-dominant hypophosphataemic rickets), but the patient had no relevant family history and was 76 years old when diagnosed. This type of hypophosphataemia could also be attributed to postrenal transplantation and iron polymaltose infusion, but neither were relevant in this case.⁵

Our patient had been treated with bisphosphonates for 3 years, which may have exacerbated his condition. However, files from his GP showed that serum levels of phosphate had been low even before this medication was started.

TREATMENT

The patient was unable to swallow any food or liquid, and a nasogastric tube was therefore inserted. Refeeding the patient was challenging due to the high risk of developing refeeding syndrome. Serum levels of potassium, calcium, magnesium and phosphate were monitored frequently, and his caloric intake was gradually augmented, starting at 10 kcal/kg/day, up to 25–30 kcal/kg/day on day 8.⁶ Even with these precautions, the patient developed biochemical changes consistent with refeeding syndrome during caloric augmentation. No clinical signs of refeeding syndrome such as dyspnoea, tachycardia, decreased oxygen saturation or oedema were found. His serum phosphate levels eventually started to increase above 0.5 mmol/L after 9 days, followed by complete resolution of his dysphagia and respiratory pain.

OUTCOME AND FOLLOW-UP

Six weeks after discharge, the patient ate well, had gained 10 kilograms, had no signs of dysphagia and had an overall higher function. For months, the patient required the maximum dose of oral phosphate supplementation (3 g/day). By increasing both calcitriol and calcidiol intake together with phosphate, he was able to reduce

the dose. This was important for managing diarrhoea, which had become almost intolerable after starting oral phosphate substitution. One year after discharge, serum phosphate was normalised at 0.8 mmol/L for the first time in many years (see [table 1](#)). The patient now had remarkably good function and a stable weight. His bone pain was reduced and he reported increased quality of life. We did Octreotide-scintigraphy, MIBG-scintigraphy and a positron emission tomography scan to detect other potential tumours, but no other tumours were found.

DISCUSSION

Our patient with severe hypophosphataemia presented with several symptoms: malnutrition, dysphagia, respiratory pain, muscle weakness and multiple fractures over many years. Observing a poor response to high doses of phosphate supplements, we started further systematic investigation, focusing on phosphate distribution, intestinal absorption and renal excretion. Hypophosphataemia is usually caused by one or more of the following three mechanisms:

1. Altered distribution between the intracellular and extracellular compartments. This is typically seen in malnutrition and refeeding syndrome causing rapid intracellular influx of phosphate. Our patient was malnourished, but in refeeding syndrome, it is usually not difficult to reach normal levels of serum phosphate when increasing phosphate supplies. In refeeding syndrome, phosphate levels are often normal during the initial phase and drop after introducing food. In our case, baseline serum phosphate levels were extremely low, measured at 0.1 mmol/L.
2. Impaired intestinal uptake. Our patient did not have any sign of malabsorption and there were normal levels of 25-hydroxy-vitamin D.
3. Increased urinary excretion. Normally, about 180 mmol of phosphate is filtered through the glomerulus every 24 hours. In phosphate deficiency, tubular reabsorption is pronounced and less than 5% is excreted in the urine. In our patient, we estimated renal phosphate loss at 49 mmol/L per day, which is unusually high, especially when concurrent serum phosphate levels are below 0.3 mmol/L. Several studies have shown that hypophosphataemia may be associated with phosphaturic substances such as FGF-23, which increases urinary excretion. Increased levels of such substances are commonly seen in mesenchymal tumours such as paragangliomas.^{7,8} Shortly after surgical removal of these tumours (ie, within hours), serum phosphate levels start to normalise.

It is assumed that this patient's condition was not typical osteoporosis, but rather an osteomalacia caused by low levels of phosphate over many years. Because of this, normal ossification had not been occurring. We discontinued bisphosphonates early because a side effect is increased renal excretion of phosphate. A serum phosphate level of 0.1 mmol/L induced by bisphosphonates alone has not been previously described. In this patient,

we also found low levels of serum phosphate as early as 2012 (before introduction of bisphosphonates). Recent studies have suggested that FGF-23 has a direct action of reducing mineralisation of the bones,⁹ which could explain why he has had more frequent fractures than would be expected in other forms of hypophosphataemia.

The patient was admitted to hospital with severe dysphagia. He even had major difficulties swallowing water and his own saliva. The dysphagia might be associated with his profound hypophosphataemia. Intracellular ATP levels fall with severe hypophosphataemia, and cell functions dependent on energy-rich phosphate compounds begin to fail. Manifestations of muscle dysfunction include a proximal myopathy and dysphagia.¹⁰

Unlike other conditions, in which dysphagia and the resulting malnutrition are typically progressive and irreversible, these symptoms rapidly disappeared when the serum phosphate increased in this patient, even without removal of the tumour.

Our patient had extensive cardiovascular disease, and therefore surgical removal of the tumour was not recommended. We chose a conservative approach of supplementing with phosphate and vitamin D compounds. Somatostatin receptors have been

found to be present in many tumours leading to tumour-induced osteomalacia.^{11 12} Treatment with somatostatin analogues would have been an alternative form of treatment for this patient had the substitution therapy failed. Many of the patients receiving both high doses of phosphate and active vitamin D will develop reactive hypercalcaemia, which can be treated with the calcimimetic substance Cinacalcet. In the first year after diagnosis, this has not been necessary in this patient.

Contributors All authors have participated in writing the article. We have all treated the patient during investigations, treatment or follow-up. We have discussed the case through several meetings. JV and MP have contributed with important findings during both investigation, treatment and follow-up. PG has also contributed with excellent expertise as a senior physician. TR, the first author, has been responsible for connecting all contributions together.

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Learning points

- ▶ Severe hypophosphataemia that does not respond well to supplements should raise clinical alertness. The condition might be tumour-induced and can become fatal.
- ▶ Dysphagia, malnutrition and general weakness are non-specific symptoms. Seen together with profound hypophosphataemia, these might be associated with ATP depletion and muscle weakness and may be reversible with proper treatment.
- ▶ Refeeding a severely malnourished patient with initial profound hypophosphataemia is demanding and requires close monitoring, both biochemically and clinically.
- ▶ The patient's medications should be reviewed, stopping any medications that could be a potential contributing factor.
- ▶ Measuring urinary phosphate excretion and phosphaturic substances such as fibroblast growth factor 23 and conducting further examinations with CT and scintigraphy are recommended to diagnose tumour-induced osteomalacia. Surgical removal of the tumour might alleviate the condition. If the tumour is inoperable, lifelong substitution of phosphate and 1,25-dihydroxy-vitamin D might be necessary.

REFERENCES

- 1 Gaasbeek A, Meinders AE. Hypophosphatemia: an update on its etiology and treatment. *Am J Med* 2005;118:1094–101.
- 2 Jan de Beur SM. Tumor-induced osteomalacia. *JAMA* 2005;294:1260–7.
- 3 Dey B, Gochhait D, Subramanian H, et al. Oncogenic osteomalacia: an approach to diagnosis with a case report. *J Clin Diagn Res* 2017;11:ED05–7.
- 4 Stubbs J, Liu S, Quarles LD. Role of fibroblast growth factor 23 in phosphate homeostasis and pathogenesis of disordered mineral metabolism in chronic kidney disease. *Semin Dial* 2007;20:302–8.
- 5 Imel EA, Econs MJ. Approach to the hypophosphatemic patient. *J Clin Endocrinol Metab* 2012;97:696–706.
- 6 National Institute for Health and Care Excellence. Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition. NICE Clinical guideline CG32, 2006. 2017 <https://www.nice.org.uk/guidance/cg32>
- 7 Hautmann AH, Hautmann MG, Kölbl O, et al. Tumor-Induced Osteomalacia: an Up-to-Date Review. *Curr Rheumatol Rep* 2015;17:512.
- 8 Carpenter TO. Oncogenic osteomalacia—a complex dance of factors. *N Engl J Med* 2003;348:1705–8.
- 9 Imanishi Y, Hashimoto J, Ando W, et al. Matrix extracellular phosphoglycoprotein is expressed in causative tumors of oncogenic osteomalacia. *J Bone Miner Metab* 2012;30:93–9.
- 10 Alsumrain MH, Jawad SA, Imran NB, et al. Association of hypophosphatemia with failure-to-wean from mechanical ventilation. *Ann Clin Lab Sci* 2010;40:144.
- 11 Duet M, Kerkeni S, Sfar R, et al. Clinical impact of somatostatin receptor scintigraphy in the management of tumor-induced osteomalacia. *Clin Nucl Med* 2008;33:752–6.
- 12 Houang M, Clarkson A, Sioson L, et al. Phosphaturic mesenchymal tumors show positive staining for somatostatin receptor 2A (SSTR2A). *Hum Pathol* 2013;44:2711–8.

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