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CASE REPORT

Oncogenic osteomalacia and metastatic breast cancer: a case report and review of the literature

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Abstract

Objectives Oncogenic osteomalacia is a rare paraneoplastic metabolic syndrome that is characterised by severe hypophosphataemia, hyperphosphaturia and osteomalacia secondary to renal loss of phosphate. It is commonly caused by overproduction of fibroblast growth factor-23 (FGF23) from benign tumours of mesenchymal origin. Currently, there is no clear evidence on the management of oncogenic osteomalacia in patients with metastatic solid tumours.

Methods We report a case of breast cancer-induced oncogenic osteomalacia and discuss its diagnosis and management.

Results A 71-year-old woman with advanced breast cancer developed symptomatic oncogenic osteomalacia with raised FGF23, severe hypophosphataemia and hypocalcaemia. The electrolytic disturbances were exacerbated after the administration of bisphosphonates in the context of her oncological treatment. Systemic chemotherapy and maintenance endocrine treatment along with phosphate and calcium supplementation reduced the activity of oncogenic osteomalacia and resolved the electrolytic imbalances.

Conclusions To our knowledge, this is the first reported case of oncogenic osteomalacia in a patient with breast cancer. Oncogenic osteomalacia constitutes a diagnostic and therapeutic challenge. Pre-clinical and clinical evidence suggest that a possible underlying mechanism is the presence of molecular alterations in the FGF/FGFR signalling pathway leading to overexpression of FGF23. In metastatic setting, anticancer treatment can potentially lead to the normalisation of the electrolytic disturbances and reduction of the activity of oncogenic osteomalacia. The use of antiresorptive therapy in patients with bone metastases can potentially trigger FGF23 overexpression. Its use should be guided by the patients' risk of skeletal-related events and electrolytic disturbances as well as the degree of activity of oncogenic osteomalacia.

Keywords Tumour-induced osteomalacia · Breast cancer · Hypocalcaemia · Hypophosphataemia

Introduction

Oncogenic osteomalacia is a rare paraneoplastic metabolic bone disease, which is characterised by renal loss of phosphate [1, 2]. The incidence is largely unknown but more than 300 cases have been reported in the literature [3]. Oncogenic osteomalacia is commonly associated with tumours of mesenchymal origin that secrete the fibroblast growth factor-23 (FGF23), a vitamin D- and phosphate-regulating hormone [4]. This is the first reported case of breast cancer-induced oncogenic osteomalacia. This case constitutes a diagnostic and therapeutic challenge since the oncological management of metastatic breast cancer involves not only chemotherapy and/or endocrine therapy but also bone protection, such as zoledronic acid or denosumab, which can exacerbate the electrolytic abnormalities caused by oncogenic osteomalacia.

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Case presentation

A 71-year-old woman presented 2 years ago with recurrent metastatic oestrogen receptor (ER) positive and human epidermal growth factor receptor 2 (HER2) negative breast cancer with bone metastases and bone marrow infiltration. She received 3 cycles of weekly paclitaxel chemotherapy as well as two cycles of zoledronic acid as a part of her oncological treatment. The patient developed symptomatic electrolytic disturbances with severe hypophosphataemia and hypocalcaemia after she had received zoledronic acid infusion. She had a previous history of early primary breast cancer in 2004 that was treated with wide local excision followed by mastectomy and breast reconstruction. She received adjuvant anastrozole for 5 years. Her medications included ranitidine, amitriptyline and solifenacin. She is a non-smoker and does not consume alcohol. There was no family history of malignancy.

The initial laboratory investigations after her first cycle of zoledronic acid showed hypophosphataemia at <0.32 mmol/l (0.80–1.45 mmol/l), hypocalcaemia at 1.93 mmol/l (2.20–2.60 mmol/l), elevated alkaline phosphatase (ALP) at 250 U/l (40–130 U/l), increased parathyroid hormone (PTH) at 343 ng/l (18–80 ng/l), normal 25 Hydroxyvitamin D (25-HD) at 84 nmol/l (24–167 nmol/l) and normal 25-dihydroxyvitamin D (1,25-DHD) at 57 pmol/l (20–120 pmol/l). The complete blood count, liver and renal function tests were all normal. Serum FGF23 was raised at 311 u/ml (normal 0–100 u/ml) which was consistent with oncogenic osteomalacia. The tumour markers were Ca-153 at 4235 ku/l (normal 0–35 ku/l) and carcinoembryonic antigen (CEA) was 115 μg/l (normal 0–3 μg/l) at diagnosis. The baseline staging CT thorax abdomen and pelvis showed extensive bone metastases and the bone marrow trephine biopsy revealed metastatic adenocarcinoma. All the relevant investigations throughout her oncological management are summarised in Table 1.

The electrolytic disturbances were managed by discontinuing the zoledronic acid infusions and by initially administrating calcium and phosphate infusions. After the phosphate and calcium were normalised the patient was commenced on oral calcium and phosphate supplements. She received weekly paclitaxel chemotherapy (80 mg/m2 IV infusion, Day 1, 8 & 15), an antimitotic agent which promotes microtubule stabilisation, thereby inhibiting disassembly required for mitosis. After completing 3 cycles of paclitaxel chemotherapy she was commenced on maintenance endocrine therapy fulvestrant, a subcutaneous oestrogen receptor antagonist that is administered 500 mg intramuscularly (IM) 4-weekly after an initial loading dose of 500 mg IM 2-weekly for three doses.

Chemotherapy, the subsequent maintenance endocrine therapy and oral phosphate and calcium supplements, resulted in the normalisation of the serum electrolytes and an improvement of the FGF23, ALP and PTH (Table 1). The tumour markers Ca-153 and CEA improved significantly and the three monthly restaging CT thorax, abdomen and pelvis scans showed stable disease. Nevertheless, 18 months later, a gradual increase in the tumour markers was observed with stable disease in the restaging CT thorax abdomen and pelvis. Otherwise, she was asymptomatic with no history of bone pain or any other cancer-related symptoms. Although the latest FGF23 was improving at the value of 121, it was still raised indicating that the patient still has had active oncogenic osteomalacia. The rest of the bone profile was normal. At this stage, we considered denosumab, a monoclonal antibody, which inhibits the human receptor activator of nuclear factor kappa-B ligand (RANKL). Nonetheless, denosumab was withheld because it could potentially cause severe

Table 1 Oncological management and laboratory investigations

	06/2016	07/2016§	08/2016	09/2016¶	11/2016	02/2017	05/2017	01/2018	03/2018
Oncological treatment	CT	CT & Z	CT	CT & Z	CT	ET	ET	ET	ET
FGF23 (u/ml)	–	–	–	–	311	146	146	121	–
ALP (U/L)	138	250	353	144	136	173	105	96	108
PTH (ng/l)	343	–	176	322	406	59	61	52	–
25-HD (nmol/l)	52	–	66	84	57	–	69	79	–
Calcium (mmol/l)	1.85	1.93	2.11	1.91	2.11	2.17	2.24	2.34	2.20
Phosphate (mmol/l)	0.60	<0.32	0.41	0.49	0.70	1.27	1.29	1.02	1.03
Ca153 (ku/l)	4235	–	4019	–	2632	1524	1220	1430	1531
CEA (μg/l)	115	–	117	–	76	80	87	123	134

Abbreviations: CT chemotherapy, *Z* zoledronic acid, *ET* endocrine treatment, *FGF23* fibroblast growth factor 23, *ALP* alkaline phosphatase, *PTH* parathyroid hormone, *25-HD* 25-hydroxyvitamin D, *CEA* carcinoembryonic antigen

§ results obtained 6 days after the administration of zoledronic acid; ¶ results obtained 3 weeks after the administration of zoledronic acid

hypocalcaemia and hypophosphataemia on the background of active oncogenic osteomalacia [5].

Discussion

Oncogenic osteomalacia is a rare paraneoplastic syndrome that causes severe hypophosphataemia, hyperphosphaturia and osteomalacia secondary to renal loss of phosphate [6]. Secondary hyperparathyroidism may also occur as a normal feedback response to low 1, 25-DHD levels [1]. Furthermore, ALP is elevated due to increased osteoblastic activity. In patients with oncogenic osteomalacia, raised FGF23 exerts phosphaturic action in proximal tubule cells by decreasing renal tubular phosphate reabsorption. This effect is mediated via the FGF receptors (FGFR) 1, 3 and 4 as well as the co-receptor Klotho that are expressed in proximal renal tubules [2]. This downregulates the expression of type II sodium-phosphate co-transporters which are found in the proximal tubule resulting in the inhibition of the renal phosphate reabsorption and increased renal excretion of the phosphate [2]. FGF 23 regulates 1,25-DHD by suppressing the alpha hydroxylase [7, 8]; rising 1,25-DHD stimulates FGF23 and downregulates the alpha hydroxylase expression in a classical endocrine fashion [9].

Under physiological conditions, FGF23 is secreted by osteoblasts and osteocytes and its secretion is supressed by proteolytic enzymes such as the phosphate regulating endopeptidase homolog on the X chromosome (PHEX) as well as matrix-associated proteins, all of which are expressed in the bone [6, 10]. Nevertheless, in the case oncogenic osteomalacia, tumours secrete FGF23 in hundredfold levels compared to the normal limits [11]. The oversecretion of FGF23 overwhelms the degradation process, inhibits renal phosphate absorption and reduces 1,25-DHD synthesis [11, 12]. These lead to phosphaturia and reduced intestinal absorption of calcium and phosphate, respectively. Hence, the combination of phosphate loss and reduced 1,25-DHD synthesis results in hypophosphataemia and osteomalacia [11].

Tumour-induced osteomalacia usually presents with progressive, generalised bone pain, muscle weakness, myalgia or myopathy in chronic cases [3]. Radiological findings may include signs of osteopenia such as Looser-Milkman zones or multiple pseudofractures or osteoporotic fractures especially in the pelvis and lower limbs [13]. Oncogenic osteomalacia is commonly associated with soft tissue or bone malignancies, which constitute a distinct entity called phosphaturic mesenchymal tumours (PMTs) [3]. PMTs are usually small, benign and characterised by low grade and mitotic index, requiring PET imaging to be detected [3]. However, it has also been linked with malignant haematological and solid tumours such as leukaemia [14], head and neck cancer [15], B cell non-Hodgkin's lymphoma [16], sarcoma [17], anaplastic thyroid carcinoma [18], small cell lung cancer [19], prostate cancer [20] and adenocarcinoma of the colon [21].

In cancer, abnormal FGF signalling has been shown to induce cell proliferation, enhance motility, invasiveness and angiogenesis, evade apoptosis, promote metastasis and resistance to anticancer treatment [22]. Impairment of this signalling pathway can occur via different pathophysiological mechanisms such as amplification of FGFs/FGFRs, mutations in FGFRs, translocations and loss of feedback control [22]. In breast cancer, amplification of FGFR1 and FGFR2 receptors are the most commonly seen molecular alterations with a frequency of 10.8% and 1.9%, respectively [22, 23]. Activating mutations, FGFR1 and FGFR2 translocations and isoform switching are less frequent [22–24].

These molecular alterations, lead to the increased transcription, translation and secretion of FGF23 by tumour cells via positive autocrine feedback loop [10]. Specifically, amplifications and translocations can lead to autodimerisation inducing ligand-independent signalling. In addition, translocations can also result in the production of chimeric FGFRs such as FGFR1 that can either dimerize and bind to FGF23 and transduce signal in a klotho-independent manner or dimerize with klotho in the presence of FGF23 and transduce in a klotho-dependent manner within the tumour microenvironment [10, 24, 25]. Furthermore, preclinical breast cancer models demonstrated that aberrant autocrine and paracrine positive feedback loops involve FGFRs and FGFs ligands such as FGFR1 and FGF2, respectively, which result in increased secretion of FGFs by the tumour or stromal cells [26]. This was supported by Xaio L et al. who showed that FGF2 isoform in murine osteoblasts cultures activates directly the FGFR pathways, which in turn increase the production of FGF23 [27]. Furthermore, selective blockade of FGFRs inhibits FGF23 secretion in Hyp-derived bone marrow stromal cell cultures [25].

The role of FGF/FGFR1 signalling pathway in breast cancer-induced oncogenic osteomalacia was also shown in clinical trials of novel tyrosine kinase inhibitors targeting the FGF signalling. Specifically, in phase I trials that included FGFR1-amplified breast cancer patients and evaluated the safety and efficacy of BGJ398, a selective FGFR1–3 inhibitor and JNJ-42756493, a pan-FGFR inhibitor, showed that hyperphosphataemia was the most common adverse effect [24, 28]. Furthermore, in the context of a phase II trial, two patients mesenchymal tumour-induced oncogenic osteomalacia received BGJ398 inhibitor and demonstrated not only significant radiological and biochemical response but also reduction of the activity of oncogenic osteomalacia [29]. These findings indicate that the development of oncogenic osteomalacia in patients with breast cancer can be attributed to the FGFR molecular alterations within the tumour microenvironment, which in turn enhance the FGF signalling, leading to increased FGF23 production in an FGFR-dependent manner.

In this case, the diagnosis of oncogenic osteomalacia on clinical grounds is uniquely challenging on a background of a patient with metastatic cancer. The biochemical findings of hypophosphataemia may also be multifactorial in this setting and include reduced dietary intake, vomiting or diarrhoea from primary disease or cytotoxic treatments or treatment with zoledronic acid. Although zoledronic acid could have potentially caused severe hypophosphataemia, we would expect normal PTH and FGF23. In addition, the biochemical abnormalities were present prior to the administration of zoledronic acid (Table 1) and consequently the latter might have contributed rather than caused the electrolytic disturbances. This case was initially treatment-refractory most like due to massive renal phosphate losses secondary to oncogenic osteomalacia [5]. Vitamin D deficiency could be a possible cause for this biochemical picture**.** Nevertheless, we would expect low 25-HD and low or normal 1,25-DHD as well as normal or low levels of FGF23 [10]. Phosphate deficiency is another possible explanation, however in this case raised FGF23 was not consistent with phosphate deficiency [10]. Furthermore, cytotoxic drugs, such as cisplatin, can cause a range of nephrotoxicity, which commonly includes acute kidney injury and hypomagnesaemia, however a fanconi-like syndrome has also been reported [30]. Nonetheless, single agent paclitaxel chemotherapy, which was given to this patient, has not been reported to cause hypophosphataemia or phosphaturia.

In a broader cohort of patients, the differentials can be divided into acquired and inherited. Acquired causes of hypophosphataemia result from renal tubular damage and include iatrogenic causes such as aminoglycoside antibiotics and anti-retrovirals, refeeding syndrome and monoclonal gammopathies [31]. Fanconi syndrome, which causes renal tubular defects, can be differentiated by its normal FGF23 levels and more profound accompanying electrolyte abnormalities such as to sodium, potassium, bicarbonate, glucose and uric acid as well as metabolic acidosis [9, 31]. Early stages of chronic kidney disease can also increase circulating FGF23 levels and result in hypophosphataemia before a general decline in levels of renal function [9]. An inherited cause should be considered in a child or young adult with this presentation where conditions such as autosomal dominant hypophosphataemic rickets, X-linked hypophosphataemia, autosomal recessive hypercholesterolaemia rickets and autosomal recessive hypophosphataemia should be considered [9].

In patients with early stage tumour, complete surgical resection of the tumour is the treatment of choice [1]. A biochemical improvement of the phosphate levels is usually noticed within 2–10 days of surgery [1]. However, it may take several months for the resolution of the clinical symptoms and there is usually a permanent bone sequela [1]. In patients with metastatic disease, treatment includes oral supplements of phosphate and calcium [3]. In addition, anticancer systemic treatment such as chemotherapy or targeted therapy or radiotherapy for locally advanced inoperable or metastatic tumours may lead to clinical and biochemical improvement of the oncogenic osteomalacia [3, 21]. The use of somatostatin receptor agonist such as octreotide as well as cinacalcet, which is a calcium-sensing receptor agonist or monoclonal antibodies against FGF23 and its receptor, constitute promising targeted treatments [1, 3].

Breast cancer patients with bone metastases frequently undergo bone-targeted therapy with either bisphosphonates or denosumab. It is known that denosumab and bisphosphonate are associated with reduced risk of skeletal-related events, improved health-related quality of life and reduction of pain intensity in these patients [32]. Nonetheless, the use denosumab and bisphosphonates can be associated with electrolytic disturbances such as hypocalcaemia and hypophosphataemia [33, 34]. Currently, there is no clear evidence on the impact of bisphosphonates or denosumab in patients with bone metastases on the background of oncogenic osteomalacia.

Mild and transient hypophosphatemia constitutes a common side effect of denosumab and zoledronic acid [5]. Under physiological conditions, this constitutes a homeostatic response to hypocalcaemia where the latter leads to the secretion of PTH in order to maintain normocalcaemia. Then, PTH-induced 1,25-DHD induces FGF23 secretion which in turn results in phosphaturia [5]. Furthermore, FGF23 can exert an autocrine function by activating FGFR1, which in turn increases the expression of FGF23 via a positive feedback loop [5]. Hence, in patients with cancer and underlying oncogenic osteomalacia, antiresorptive therapy may potentially trigger the positive FGF23-FGFR1 feedback loop initiating in this way the overexpression of FGF23 [5].

These results should be interpreted in the light of certain limitations. Specifically, the 24-h urine phosphate excretion was not determined, which is important for confirming oncogenic osteomalacia. However, the patient had had several months of hypophosphatemia, ill health with weight loss and she was treated with phosphate and calcium supplements. Hence, the interpretation of the phosphate excretion results in this case would be challenging [35].

Conclusions

To our knowledge, this is the first published case of oncogenic osteomalacia in a patient with metastatic breast cancer. Oncogenic osteomalacia is a diagnostic and therapeutic challenge. Pre-clinical and clinical evidence suggest that the most likely underlying mechanism is the presence of molecular alterations in the FGF/FGFR signalling pathway within the tumour microenvironment leading to increased synthesis of FGF23. In metastatic setting, systemic oncological treatment can potentially normalize the levels of serum phosphate,

reduce the activity of oncogenic osteomalacia and improve the symptoms. The use of antiresorptive treatment in patients with bone metastases can potentially trigger FGF23 overexpression. For this reason, its use should be guided by the patients' symptoms, risk of skeletal-related events and electrolytic disturbances as well as the degree of activity of oncogenic osteomalacia.

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Compliance with ethical standards

The authors declare that they did not have any industrial links of affiliations.

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Written informed consent was obtained from the patient for publication of this case report.

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