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SHORT COMMUNICATION

Advanced prostate cancer as a cause of oncogenic osteomalacia: an underdiagnosed condition

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Abstract
Purpose Tumor-induced osteomalacia (TIO) is a paraneoplastic bone mineral disturbance related to fibroblast growth factor 23 (FGF23) overproduction by the tumor, usually from mesenchymal origin. Such condition leads to high phosphate renal wasting and, consequently, to cumbersome symptoms as weakness, bone pain, and fractures.
Method Case report.
Result We report a case of an advanced castration-refractory prostate cancer patient, which developed severe hypophosphatemia with elevated phosphate excretion fraction. TIO was suspected, and increased levels of FGF23 reinforced such diagnosis. The patient died 4 months after being diagnosed with TIO.
Conclusion This case suggests that TIO has a dismal prognosis in prostate cancer patients. The clinical oncology community must be aware about such disturbance that can be present in those patients with weakness, bone pain, and hypophosphatemia.

Keywords Tumor-induced osteomalacia · Prostate cancer · Bone metastasis · Hypophosphatemia · FGF23

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Introduction

Bone mineral disturbances are a common finding in advanced prostate cancer, usually as a consequence of extensive metastatic disease [1]. Generalized bone demineralization with disabling weakness, bone pain, and fractures, a condition known as osteomalacia, is frequently seen in advanced cancer patients, usually as a consequence of malnutrition and vitamin D deficiency.

In these patients, another rare reason for osteomalacia is the fibroblast growth factor 23 (FGF23) overproduction by the tumor, leading to an increased phosphate wasting, a condition known as tumor-induced osteomalacia (TIO), presenting with disabling weakness, bone pain, and fractures, which is commonly underdiagnosed [2–5]. We report a case of a 69-year-old patient with advanced castration-refractory prostate cancer, in which TIO contributed significantly to his clinical deterioration.

Case report

A 63-year old male patient was diagnosed with a Gleason 6 (3+3) prostate adenocarcinoma in 2003, staged as T_2 N_0 M_0, when a radical prostatectomy was performed, with tumor-free margins. Biochemical recurrence was verified after 1 year (prostate specific antigen (PSA), 7.6 ng/mL), which was treated with salvage radiation therapy in prostate

bed and gonadotropin-releasing hormone analogs from 2004 to 2008.

In October 2008, he presented with painful, disseminated bone metastasis, according to bone and computed tomography scans, and a PSA level of 421 ng/mL under castration, characterizing a castration-refractory disease. PSA rising was observed despite combining a peripheral antiandrogen (bicalutamide). In January 2009, he was enrolled in a clinical trial evaluating the specific endothelin A receptor antagonist zibotentan (formerly known as ZD4054; AstraZeneca, Macclesfield, UK) in association with docetaxel and prednisone (ENTHUSE 33, ClinicalTrials.gov identifier NCT00617669). Symptomatic improvement was observed, as well as biochemical response throughout the first seven cycles of docetaxel (PSA decreased from 465 to 157 ng/mL).

Hypophosphatemia (2.1 mg/dL; normal range 2.7–4.5 mg/dL) was first diagnosed in December 2008 and, initially, was considered as clinically nonsignificant. After the sixth cycle of chemotherapy, the patient developed symptomatic hypophosphatemia (0.9 mg/dL) that was corrected with intravenous phosphorous replacement.

After the seventh cycle of chemotherapy, the patient was admitted due to a 2-month history of worsening pain in his upper and lower limbs and rising PSA levels (206 ng/mL). He presented a flaccid tetraparesis which was attributed to a severe hypophosphatemia (0.8 mg/dL). Intravenous phosphate was initiated and after achieving a serum phosphate level of 2.2 mg/dL, a significant improvement was noticed, and all complaints remitted. Additional work-up revealed an increased phosphate excretion (54 %; normal, <5 %), a parathyroid hormone (PTH) level of 108 pg/mL (normal range 16–87 pg/mL), 25-hydroxy-vitamin D level of 17 ng/mL (recommended is >30 ng/mL), as well as hypocalcemia (ionized calcium 4.2 mg/dL; normal range 4.6–5.3 mg/dL), which was initially attributed to chemotherapy. An oral supplementation of 30 mg/kg/day of elemental phosphate, 1,000 IU/day of cholecalciferol, and 1.5 g/day of calcium were initiated, and the patient was discharged with full symptom recovery.

Chemotherapy was interrupted and prednisone 5 mg twice a day orally was maintained. After 4 months, the patient was again admitted with flaccid tetraparesis and worsening limb pain, but now with delirium and deterioration of performance status (Eastern Cooperative Oncology Group (ECOG) performance status 4). A 0.8 mg/dL serum phosphate was noticed, and he maintained high phosphate excretion fraction (61 %), hypocalcemia (ionized calcium 4.2 mg/dL), and low 1,25-dihydroxy-vitamin D level (12 pg/mL; normal range18–72 pg/mL). PTH level was 105 pg/mL. Intravenous phosphate replacement was initiated, and considering that he had not received any chemotherapy after his last hospitalization, drug-related hypophosphatemia was unlikely. Other abnormalities in proximal reabsorption were not detected, except higher phosphaturia, and considering that a low plasmatic level of 1,25-dihydroxy-vitamin D was present, TIO was suspected. In the context of osteomalacia in a patient with disseminated bone metastasis, we have decided not to perform a bone biopsy considering the palliative intent of the treatment.

In order to further support our hypothesis, we performed a FGF23 determination, which was revealed as increased (176 pg/mL; normal range 10–50 pg/mL; Kainos Laboratories Inc., Tokyo, Japan). Calcitriol was introduced at 1.5 mcg/day orally, and a phosphatemia of 2.0–2.5 mg/dL was maintained with oral supplements of potassium and sodium phosphate (2.2 g of elemental phosphorus) and calcium carbonate (1 g of elemental calcium per day). There was an improvement of performance status (ECOG performance status 2) and a partial recovering of tetraparesis. Due to patient's wishes, he was kept under hospice care until his death, 4 months after being diagnosed with TIO.

Discussion

Tumor-induced osteomalacia, sometimes referred as oncogenic osteomalacia, is a paraneoplastic syndrome characterized by osteomalacia secondary to renal phosphate wasting, leading to severe hypophosphatemia [5]. One of the tumor-secreted factors responsible has been identified as the FGF23, a known phosphatonin. The kidney is the main target for FGF23 which inhibits both sodium-dependent phosphate resorption and 1-α-hydroxylase activity in the proximal tubule, leading to a marked urinary phosphate loss, hypophosphatemia, and inappropriately low levels of 1,25-dihydroxy-vitamin D. Serum 25-hydroxy-vitamin D and calcium levels are usually normal, but mild hypocalcemia has been described. Elevation of serum alkaline phosphatase activity is typical, and serum levels of PTH have been variably reported as low and as elevated, but are most frequently normal [4]. These patients present clinically with fatigue, bone pain, proximal myopathy, metabolic encephalopathy, and gastrointestinal disturbances (anorexia, nausea, vomiting, gastric atony, and ileus), as main consequences of severe hypophosphatemia [6].

TIO has been described in a number of tumors particularly those of benign mesenchymal origin, such as hemangiopericytoma [7]. Several reports were published in the last few years, totalizing around 200 documented cases. Less than 5 % of the cases are related to malignant tumors, such as osteosarcoma, squamous cell carcinoma, prostate cancer, and chronic lymphocytic leukemia. In such cases, hypophosphatemia may appear years before cancer diagnosis. In prostate cancer patients, since the first report in 1975 [8], around 25 additional cases of TIO have been described, and most of them are presenting with bone metastasis and castration-refractory disease.

Our patient had typical features of oncogenic hypophosphatemic osteomalacia: severe hypophosphatemia, marked phosphaturia, low 1,25-dihydroxy-vitamin D serum level, normal PTH level, and increased serum level of FGF23. Although FGF23 level (176 pg/mL) was not as high as some previous reports, it was higher than values considered to be normal in a healthy state (10–50 pg/mL). It is not clear if serum FGF23 levels correlate with the extent of the underlying cancer, the degree of phosphate wasting, or the response to treatment in metastatic prostate cancer. Although an increased FGF23 level can be suggestive, the role of other alternative phosphatonins is not yet fully characterized. Noteworthy, FGF23 assay was recently validated and is available in some centers, improving diagnosis accuracy.

In this case, the time between hypophosphatemia detection and TIO diagnosis was 6 months, demonstrating that this condition occurs late in the disease course and is underdiagnosed. In a survey of 105 patients with prostate cancer and bone metastasis, about 5.7 % of assessed patients had hypophosphatemia, which could be secondary to 25-hydroxy-vitamin D deficiency (more frequent) or TIO [6]. One should be aware of this potential complication since effective treatment can improve the health status and quality of life.

Definitive treatment for TIO is surgical excision of the tumor, if possible, which rapidly and permanently abrogates some symptoms. When tumor is not resectable, it is recommended that calcitriol (1–3 mcg/day) and oral phosphate salts (1 to 4 g/day of elemental phosphorus) be used. Normalization of serum phosphorus level may not occur, but symptoms can be minimized, and better quality of life can be achieved. Serum phosphorus above 2.0 mg/dL should be achieved if possible. Decrease in alkaline phosphatase serum levels can be a marker of treatment response. In the present case, however, since the patient had disseminated bone metastasis, such evaluation could not be conducted. Symptoms relieve in these scenarios is the main treatment goal.

It was previously reported that the treatment of prostate cancer with second line therapies can ameliorate the clinical features of TIO. Although zoledronic acid and denosumab have proven benefit in decreasing skeletal events in castration-refractory prostate cancer [9, 10], as they can further theoretically interfere with phosphate and calcium serum levels, they must be cautiously used in these patients.

In conclusion, severe hypophosphatemia whether or not related to TIO, when underdiagnosed, can be the cause of disabling symptoms, frequent hospital admissions, and negative impacts in the quality of life. In the context of osteomalacia and after excluding vitamin D deficiency, if an elevated phosphate excretion fraction is observed, FGF23 measurement allows a more accurate diagnosis of TIO. Treatment with 1,25-dihydroxy-vitamin D and oral phosphate supplementation can normalize phosphorus levels and alleviate symptoms. Although the occurrence of paraneoplastic TIO has been proposed as a poor prognostic factor in cancer, clinical data are scanty, and this aspect needs to be further explored.

Conflicts of interest The authors declare that they have no conflict of interest to disclose related to this manuscript. Here, we state that the authors have full control of all the primary data here reported, and they agree to allow the journal to review all data.

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