Six-year follow-up of a characteristic osteolytic lesion in a patient with tumor-induced osteomalacia

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Abstract

Objective: Tumor-induced osteomalacia is a rare paraneoplastic syndrome characterized by hypophosphatemia and inappropriately normal or low 1,25-dihydroxyvitamin D.

Clinical case: Here, we report a 6-year postoperative follow-up of a patient with oncogenic osteomalacia with a distinctive skeletal manifestation. The latter was characterized by an almost linear lytic lesion of a few millimeters with irregular borders, mainly involving the trabecular compartment but extending into cortical shell, located in the middle third of the right fibula. Six years after tumor resection, a sclerotic repair with a complete recovery was observed. Furthermore, we monitored a striking increase in bone mineral density throughout the observation period, reaching a peak of 73% over basal values at lumbar spine after 2 years; at total femur and radius, the peak was 47.5 and 4.6% respectively, after 4 years from tumor resection.

Conclusions: We report for the first time that an osteolytic lesion may be part of the skeletal involvement in tumor-induced osteomalacia.

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Introduction

Tumor-induced osteomalacia is a rare paraneoplastic syndrome mainly characterized, from a biochemical point of view, by hypophosphatemia, due to renal phosphate wasting, and inappropriately normal or low 1,25-dihydroxyvitamin D (1). An increased secretion of fibroblast growth factor-23 (FGF-23) is considered the pathological factor responsible for the disease (2, 3). The awareness of the disease has recently increased (4), even though no more than 300 cases have been described so far (5, 6).

While the biochemical picture of tumor-induced osteomalacia has been fully characterized, the skeletal manifestations of the disease have received little attention. Indeed, what it is generally reported is a diffuse non-specific decrease in radiodensity, coarsening of bony trabeculae and pseudofractures (7). The latter, also called Looser's zones, are considered the hallmark of osteomalacia. Interestingly, no detailed studies have been reported so far, concerning the long-term effects of removal of the tumor on

these skeletal manifestations. Here, we report a long-term postoperative follow-up of 6 years of a patient with oncogenic osteomalacia with a distinctive skeletal manifestation.

Clinical case

A 61-year-old woman was admitted to our hospital owing to a 2-year duration of generalized, severe bone pain and muscle weakness rendering her wheelchair-bound. The patient reported a history of several fractures having occurred during the past 6 years (thoracic spine (T9, T11, and T12), bilateral ischiopubic, right femoral neck, multiple ribs, clavicles, sternum, and both shoulder blades). In particular, she now complained of recent onset severe and localized pain in the right leg, unrelated to any previous trauma. Of note, she reported two episodes of nosebleed during the previous months. Her family history was negative for metabolic bone diseases. On admission, physical

Table 1 Main biochemical parameters of the patient with tumor-induced osteomalacia before and 1, 3, and 6 years after phosphaturic mesenchymal tumor resection.

Parameters	Before surgery	1 year	3 years	6 years	Normal range
s Ca	8.15	8.90	8.90	9.00	8.6–10.4 mg/dl
s P	1.10	3.65	2.75	2.50	2.5–4.5 mg/dl
s Mg	1.85	1.85	2.10	2.00	1.5–2.5 mg/dl
s Cr	0.79	0.86	0.71	0.80	0.5–1.2 mg/dl
s ALP	553	280	193	275	80–275 U/l
s BALP	118	38	29	43	15–43 U/l
s 25(OH)D	25	25	22	39	> 20 ng/ml
s 1,25(OH) ₂ D	15.6	55.4	77	62.3	20–67 pg/ml
s PTH	53	71	63	66	10.6–54 pg/ml
s FGF-23	123	13			< 50 pg/ml
CrCl	120	115	112	115	60–120 ml/min
u Ca	228	263	192	248	50–300 mg/24 h
u P	763	636	615	723	300–1000 mg/24 h
u β-CTX	975	702			34–992 μg/mMCr
s β-CTX			0.78	0.14	0.14–1.35 ng/ml
TmPO ₄ /GFR	0.06	2.6	2.5	2.6	2.5–4.2

s, serum; u, urine; Ca, calcium; P, phosphorus; Mg, magnesium; Cr, creatinine; ALP, total alkaline phosphatase; BALP, bone alkaline phosphatase; PTH, parathyroid hormone; FGF-23, fibroblast growth factor 23; CrCl, creatinine clearance; β-CTX, C-terminal cross-linking telopeptide of type I collagen; TmPO₄/GFR, renal threshold phosphate concentrations.

examination was unremarkable with the exception of a slight increase in vertebral curvature and a referred pain, which augmented with the pressure, on the middle third of the right leg; neurological examination as well as neurological imaging studies was negative. The bone mineral density (BMD) values measured at lumbar spine, hip, and radius by dual-energy X-ray absorptiometry (Hologic QDR 4500A) (8) were low (lumbar spine 0.745 g/cm², *T*-score −2.7; femoral neck 0.552 g/cm², *T*-score −2.7; total femur 0.543 g/cm², *T*-score −3.3; one-third of the radius 0.473 g/cm², *T*-score −3.7; total radius 0.388 g/cm², *T*-score −3.5). Laboratory tests (Table 1) (9, 10, 11) suggested renal phosphate wasting, consistent with the diagnosis of hypophosphatemic osteomalacia. An initial X-ray examination performed to investigate the nature of right leg pain revealed an almost linear lytic lesion of a few millimeters with irregular margins mainly involving the trabecular compartment but extending into cortical shell, on the middle third of the right fibula (Fig. 1). T1-weighted images of magnetic resonance imaging of the fibula showed a thin hypointense rim, extending from the spongiosa to the cortical envelope (Fig. 2). Due to the uncertain nature of this lesion, a computed tomography-guided biopsy of the fibula was suggested, which was not possible to perform due to the very small size of the lytic lesion in a long, thin bone. Then, a magnetic resonance image of the maxillofacial region was performed following the otolaryngologist consultation; this revealed a thickening, probably originating from the mucosa of the left mean nasal turbinate and protruding into the lumen of the nasopharyngeal area, about 1.5 cm in

diameter. A scintigraphy with ¹¹¹Indium-pentetreotide as a tracer, according to standard techniques, detected a lesion in the nasopharyngeal area, without uptake in the right leg. A full-body positron emission tomography/computed tomography localized the nasopharynx lesion but not the fibula lesion. Therefore, the nasopharyngeal lesion was removed by endoscopy and the microscopic examination documented a phosphaturic mesenchymal tumor (mixed connective tissue variant). Tumor resection led to improvement of biochemical parameters (Table 1) together with striking increase in BMD. Indeed, at lumbar spine, a

Figure 1

Radiograph of the right leg. A linear lytic lesion (arrow) of a few millimeters with irregular margins, mainly involving the trabecular compartment but extending into cortical shell, on the middle third of the right fibula. A magnification of the lesion is shown on the right side.

Figure 2

T1-weighted images of magnetic resonance imaging of the fibula, showing a thin hypointense rim (arrows), extending from the spongiosa to the cortical envelope.

peak of 73% over basal values was reached after 2 years; at total femur and radius, the peak was 47.5 and 4.6% respectively, after 4 years from tumor resection. At the end of 6 years, the final increment was 39.2% at lumbar spine and 42.7% at total femur, while the radius registered a decrease of 1.8% (Fig. 3).

Interestingly, the right leg pain regressed in a few months; 1 year later, the X-ray examination revealed that the osteolytic lesion in the fibula disappeared, being replaced by a sclerotic focal area deforming the cortical profile of the bone. The same picture was observed 3 and 6 years later (Fig. 4). After the operation, the patient was treated with 50.000 IU cholecalciferol weekly for 3 months and then with 800 IU on a daily basis. During the first postoperative year, a supplement of 1.000 mg of elemental calcium was added to the usual diet.

Discussion

Our patient represents a typical case of tumor-induced osteomalacia sustained by a mixed connective tissue variant located in the nasopharyngeal area. From a skeletal point of view, she suffered from multiple fractures, had reduced BMD, and complained of leg pain; the fibula lesion was radiologically characterized by a transverse rime of radiolucency. Regarding BMD values, a remarkable increase was observed during the 6-year follow-up; the largest and most rapid rise was detected at lumbar spine with a peak of 73%, 2 years after tumor resection. A slower, but still noteworthy increase in BMD was noticed at total femur and radius, reaching a peak of 47.5 and 4.6% respectively, 4 years after

tumor removal. The different trend of BMD increase at the various skeletal sites most probably reflects the different composition and metabolism of cortical and trabecular bone, as also observed following other therapeutic interventions (12, 13). However, to the best of our knowledge, this is the first time that such a long longitudinal observation of BMD variation has been carried out in patients with oncogenic osteomalacia. Our BMD results mirror those obtained following treatment of nutritional osteomalacia (14), even though in this last condition the rate of increase in vertebral and hip BMD seems to be more rapid in the initial few months.

We were particularly fascinated by the radiolucency rim of the fibula; an identical radiological lesion has been reported by Zura *et al.* (15) and interpreted as an insufficiency fracture or Looser's zone. This is generally described as an area of cortical lucency with surrounding sclerosis, usually perpendicular to the cortex, even though sometimes it may not go completely through the cortex. However, both Zura's and our lesions do not completely reflect this definition mainly because of involvement of both the trabecular and cortical compartments and, most importantly, because of the lack of sclerotic irregular margins. Therefore, we believe that both lesions should be diagnosed as incomplete fractures. Magnetic resonance images, showing a hypointense rim involving both spongiosa and cortical compartment, confirm our hypothesis. It is of interest that in both

Figure 3

Changes of lumbar, femoral, and radial BMD after tumor resection. The arrow indicates the date of surgery.

Figure 4

Radiograph of the right leg 1, 3, and 6 years after tumor resection. A sclerotic focal area deforming the cortical profile of the middle third of the right fibula can be seen on both anterior-posterior and lateral projections.

cases, the skeletal lesions were located in the same position of the same bone, a rising the theoretical possibility that this particular lesion may be characteristic of this hypophosphatemic disorder. Finally, it was also remarkable to note the long-term recovery of the osteolytic rim with complete remineralization.

Our report adds an important information concerning patients with tumor-induced osteomalacia; indeed, we showed for the first time that osteolytic skeletal lesions due to stress fracture may be part of the skeletal involvement in tumor-induced osteomalacia. As such, these lesions do not deserve further investigation because of spontaneous healing following tumor resection. The increase in BMD we observed is one of the most striking results reported in the literature and is determined by the mineralization of the osteoid matrix once the serum phosphate levels return to the normal range.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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