Tumor-induced osteomalacia: the importance of early diagnosis

Osteomalácia induzida por tumor: a importância do diagnóstico precoce

Camila Vieira Bellettini[1], Cristian Hirsch[1], Karen Borges de Azevedo[1,2], Ana Luiza Mattos da Silva[1,2], Tatiana Schreiber[1,2], Felipe Giovani Tawil Aubin[1,2,] Osvaldo Estrela Anselmi[2], Tatiana Freitas Tourinho[1,2]

Received from: Irmandade Santa Casa de Misericórdia de Porto Alegre, Porto Alegre, RS, Brazil.

ABSTRACT

Tumor-induced osteomalacia is a rare paraneoplasic syndrome that can be completely cured with the removal of the culprit tumor. This study described the clinical history of a patient affected by tumor-induced osteomalacia. The patient was a 57-year-old female who sought hospital due to intense and progressive pain in the lower limbs and muscle weakness, as well diffuse osteoporosis and a variety of pathologic fractures at radiographs. Laboratory tests revealed hypophosphatemia with hyperphosphaturia and raised the hypothesis of tumor-induced osteomalacia. Whole-body technetium-99m octreotide scintigraphy revealed the presence of a focal area of radiotracer uptake in the medial region of the left tarsus. After tumor excision, there was a rapid correction of serum phosphorus, reduction of musculoskeletal complaints and evidence of bone healing. Despite the diagnosis and treatment, the patient had an unfavorable clinical outcome; she developed sepsis from pulmonary focus, evolving into refractory septic shock and death. We stress the need for greater recognition of tumor-induced osteomalacia as a cause of clinical bone pain, fractures, osteopenia and muscle weakness, superimposed on the characteristic biochemical profile with hypophosphatemia and relative hyperphosphaturia. Greater awareness of the disease will allow earlier diagnosis and ultimately a greater curative potential for patients afflicted with this syndrome.

Keywords: Osteomalacia/etiology; Paraneoplastic syndromes/pathology; Hemangiopericytoma; Hypophosphatemia; Fibroblast growth factor; Early diagnosis; Case reports; Female; Middle aged

RESUMO

Osteomalácia induzida por tumor é uma síndrome paraneoplásica rara que pode ser curada completamente com a ressecção do tumor causador. Este estudo descreveu a história clínica de uma paciente afetada pela osteomalácia induzida por tumor. Paciente, de 57 anos, deu entrada no hospital por dor em membros inferiores, e fraqueza muscular intensa e progressiva, assim como osteoporose difusa e fraturas patológicas. Exames laboratoriais evidenciaram hipofosfatemia com hiperfosfatúria e levantaram a hipótese de osteomalácia induzida por tumor. Cintilografia de todo corpo com tecnécio-99m revelou a presença de área focal de captação do radiofármaco na região medial do tardo esquerdo. Após a ressecção do tumor, houve rápida correção do fósforo sérico, redução das queixas musculoesqueléticas e evidência de calo ósseo. Apesar de diagnóstico e tratamento, a paciente apresentou um desfecho clínico desfavorável, desenvolvendo sepse de foco pulmonar, choque séptico e evoluindo a óbito. Nós enfatizamos a necessidade de maior reconhecimento da osteomalácia induzida por tumor como causa de dor óssea, fraturas patológicas, osteopenia e fraqueza muscular, superpostos a um perfil bioquímico característico, com hipofosfatemia e hiperfosfatúria relativa. Maior alerta sobre a doença permitirá um diagnóstico mais precoce e maior potencial curativo aos pacientes afetados por essa síndrome.

Descritores: Osteomalacia/etiologia; Síndromes paraneoplásicas/patologia; Hemangiopericitoma; Hipofosfatemia; Fatores de crescimento de fibroblastos; Diagnóstico precoce; Relatos de casos; Humanos; Feminino; Meia-idade

INTRODUCTION

Tumor-induced osteomalacia (TIO) is a rare syndrome that leads to abnormal metabolism of phosphate and vitamin D caused by a tumor that secrete the phosphaturic hormone known as FGF-23[(1)]. TIO is characterized by complete reversal with the removal of the tumor, which is usually benign, small, mesenchymal and rarely detected during routine radiographic examination[(2)].

Due to lack of awareness of the existence of the disease, the interval between onset of symptoms and diagnosis is usually long, because of which the patient affected is generally in a debilitated state at diagnosis[(1)].

In this case report, we describe the clinical history, diagnosis and therapeutic management of a patient admitted to a hospital in Southern Brazil in April 2013 due to TIO.

1. Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, RS, Brazil.
2. Irmandade Santa Casa de Misericórdia de Porto Alegre, Porto Alegre, RS, Brazil.

Received on: 10/12/2013 – Accepted on: 26/02/2014
Conflict of interest: no

Corresponding author:
Tatiana Freitas Tourinho
Santa Casa de Misericórdia de Porto Alegre
Rua Professor Annes Dias, 295 – Centro
Zip code: 90020-090 – Porto Alegre, RS, Brazil
Tel.: 55 (51) 9992 5684 – E-mail: tatiana.tourinho@yahoo.com.br

This study was approved by the local Ethic Committee, patient's family signed a consent term and all researchers signed a commitment statement to use patient's records, ensuring the confidentiality of this work.

CASE REPORT

The patient was a 57-year-old female who sought hospital care in April 2013 due to weakness and intense pain in the lower limbs. The condition started in 2010 with progressive loss of strength in the lower limbs, which had made walking impossible a year previously. Although medical examinations had been conducted following a prior medical visit, no diagnosis was made and no treatment was provided.

She used a plaster splint during 8 months for consolidation of a fracture in the left humerus after slight trauma in September 2012. However, at admittance to hospital, the fracture was still unconsolidated. One week before admission, she presented a new fracture after a minimal trauma in the right humerus.

At admission, the patient underwent radiographs, which showed, besides bilateral diaphyseal humerus fractures, severe diffuse osteoporosis, old bilateral rib fractures, subtrochanteric fracture of the right femur and proximal diaphyseal fracture of the right tibia. Figure 1 demonstrates Looser's zone, characteristic of osteomalacia[3].

The tests to which the patient was submitted and that showed normal values were: albumin, bilirubin, creatine phosphokinase, creatinine, serum calcium, urinary calcium, serum ferritin, iron, gamma-glutamyl transpeptidase, blood count, lactate dehydrogenase, magnesium, parathyroid hormone (PTH), potassium, prolactin, C-reactive protein, plasma sodium, prothrombin time, plasma and urine electrophoresis, transaminases, urea, erythrocyte sedimentation rate, qualitative urine, anti-endomysial antibodies, anti-gliadin and transglutaminase. Thyroid function tests showed subclinical hyperthyroidism (TSH=0.26µUI/mL, T3 83 and T4=2.0ng/dL) and negative antithyroperoxidase.

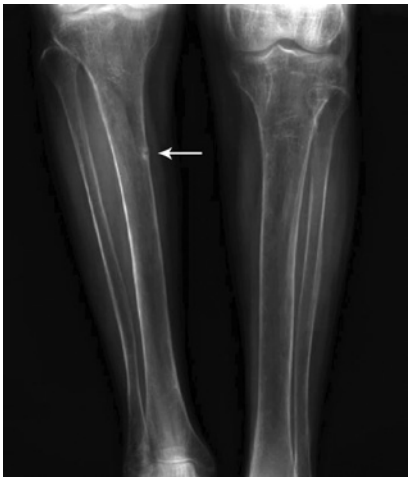

Figure 1. Arrow indicates Looser's zone in the medial tibia, consistent with the patient's symptoms of pain and diagnosis of osteomalacia.

Her medical history was marked by diagnosis of type 2 diabetes 3 years previously and hypertension. She presented no history of previous fracture, and there were no reports of osteoporosis or fractures of any kind in the family. The patient had no history of smoking or alcohol consumption. She had undergone two cesarean deliveries without further hospitalizations or surgeries.

The laboratory tests with abnormal results were: 25-hydroxyvitamin D (25(OH)D) 13ng/mL, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) (calcitriol) 22pg/mL, alkaline phosphatase 368U/L, serum inorganic phosphate 1.2mg/dL, phosphaturia 347mg/24 hours. The rate of tubular reabsorption of phosphorus was calculated to be 71.4% (normal >85%). Replacement was initiated with calcitriol and phosphate. Table 1 summarizes laboratorial investigation.

The presence of hypophosphatemia with relative hyperphosphaturia in a patient with muscle weakness and pathological fractures raised the hypothesis of TIO.

The investigation for TIO was initiated using whole-body magnetic resonance imaging (MRI). The patient underwent MRI of the skull, face, neck and chest, all without alterations. Before completing the MRI steps, whole-body technetium-99m octreotide scintigraphy (99Tcm-OCT) was made available. When performed, this revealed the presence of a small focal area of radiotracer uptake in the medial region of the left tarsus. Computed tomography (CT) images of the region, fused with the scintigraphic image, showed a small mass located medial to the tendon of the *tibialis anterior* muscle (Figure 2).

In early June 2013, tumor excision was performed. Histopathological findings corresponded to a hemangiopericytoma-type low-grade neoplasm, with foci of ossification and hemorrhage, compatible with phosphaturic mesenchymal tumor.

Following excision, pain was shown to reduce in a few days. The serum inorganic phosphorus level increased one point in 24 hours after removal (0.6 to 1.6mg/dL). It remained stable for the next few days, reaching 2.3mg/dL on the 12th postoperative day. Furthermore, there was radiographic documentation of consolidation in the old humeral fracture.

Despite the diagnosis and treatment for TIO, the patient had an unfavorable clinical outcome. On admission, she already had presented general weakness; during hospitalization, the patient developed significant malnutrition. After 3 months in

Table 1. Laboratory investigation (normal range)

Creatinine (0.3-1.3 mg/dL)	0.6
Calcium (8.0-10.5 mg/dL)	9.2
Magnesium (1.6-2.4 mg/dL)	2.2
Inorganic phosphate (2.5-5.0 mg/dL)	1.2
Alkaline phosphatase (20-130 IU/L)	368
PTH (14-72 pg/nL)	42.6
25(OH)D (>30ng/mL)	13
$1,25(OH)_2D$ (25-65pg/mL)	22
Fractional absorption of phosphate (>85%)	72%

PTH: parathyroid hormone; 25(OH)D: 25-hydroxyvitamin D; $1,25(OH)_2D$: 1,25-dihydroxyvitamin D.

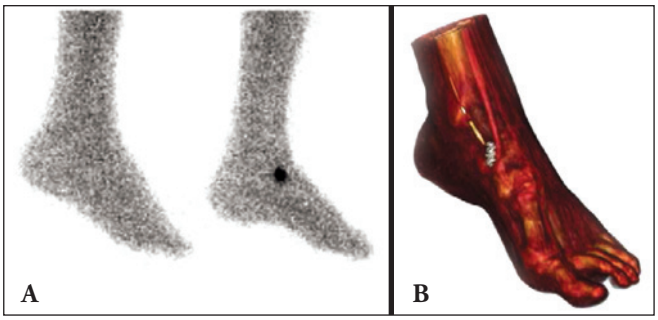

Figure 2. (A) Technetium-99m octreotide scintigraphy; (B) Technetium-99m octreotide scintigraphy fused to computed tomography imaging showing a small mass located medial to the tendon of the *tibialis anterior* muscle.

hospital, she developed sepsis from pulmonary focus, evolving into refractory septic shock, and died after 1 week in intensive care.

DISCUSSION

TIO is a rare paraneoplastic syndrome caused by mesenchymal tumors that secrete factors regulating the transport and homeostasis of phosphorus, the phosphatonins[1,2,4]. Recognized as the main cause of TIO, the phosphatonin FGF-23 acts by decreasing both tubular reabsorption of phosphorus and vitamin D activity, thus leading to changes in bone metabolism and the consequent development of osteomalacia[4-6].

The syndrome usually presents with bone pain, osteopenia, fractures and significant muscle weakness[7]. The clinical condition mimics the genetic forms of hypophosphatemia[2,8], however it onsets at an older age and with complaints of muscle weakness, severe fractures and bone pain[2] that are progressive over years[8].

The suspected diagnosis should be considered in patients with the described clinical aspects that present the characteristic biochemical profile with normocalcaemia, hypophosphatemia, hyperphosphaturia (secondary to renal waist) and increased alkaline phosphatase[7,8].

The place where hypophosphatemia is identified should have confirmation that it is caused by renal phosphate wasting[1]. This can be achieved using the formula for urinary phosphate reabsorption rate: 100x (1 - [UPO4xPCr]/ [PPO4xUCr], in which U and P are urinary and plasma concentrations of phosphate (PO4) and creatinine (Cr)[8]. There are other acquired causes of hypophosphatemia with hyperphosphaturia, such as medications (e.g., aminoglycosides, antiretroviral drugs). However, they tend to be associated with a more generalized tubulopathy, After confirming the renal phosphate wasting, other laboratory tests may also be useful in the diagnosis of TIO[1]. Vitamin D may be low or inappropriately normal. Calcium and PTH are usually normal, but PTH may be high due to secondary hyperparathyroidism, which is a normal response to vitamin-D deficiency caused by excessive FGF-23[1]. Measuring serum FGF-23 can be useful but it is not yet widely available, for which reason it was not measured in our case.

Highlighting the importance of checking the urinary excretion of glucose and amino acids[9].

The definitive treatment of the disease is obtained with complete excision of the tumor[1,2,8]. Therefore, the exact location of the tumor needs to be identified, which is a challenge given that the tumors are usually small, slow growing and frequently found in a wide variety of anatomical locations[1,8,10]. While conventional imaging methods are not very effective for this identification[2,8], somatostatin analogue scintigraphy has been shown to have great potential in locating these tumors[1,8,10,11]. This can be explained by the fact that many osteomalacia-inducing tumors express receptors for somatostatin[1,7]. In our case, the tumor was only identified with scintigraphy, having gone unnoticed even with CT. With the benefit of octreotide-assisted location, the tumor was readily detected on a second CT examination. The location of the tumor in the left foot is comparable to descriptions found in the literature, which indicate the extremities are frequently involved[8-11].

Histologically, the osteomalacia-inducing tumors are characterized by benign slow growing mesenchymal cells[8]. Less than 5% of cases of TIO are associated with malignant tumors[9]. It includes a variety of histopathological diagnoses; the most recognized being the "mixed connective tissue variant", the hemangiopericytoma[1,2,12].

The complete excision of the tumor results in immediate early correction of biochemical disorders and bone remineralization[2,8]. The biochemical profile alters in hours or a few days. Patients feel well in days to weeks following the excision, and present a normal biochemical profile in 5 to 10 postoperative days[1].

However, even after correct diagnosis and treatment, the tumor can remain obscure or incompletely resected. Then, medical management is necessary[8]. The current practice is to treat TIO with phosphorus supplementation (15 to 60mg of elemental phosphate per kg per day in four to five divided doses) in combination with calcitriol (15 to 60ng/kg per day in one to two doses)[13]. The phosphorus supplementation serves to replace ongoing renal phosphorus loss, and the calcitriol supplements replace insufficient renal production of $1,25(OH)_2D$ and the enhance renal and gastrointestinal phosphorus reabsorption[8].

In our experience, there was an evident rapid correction of serum phosphorus, reduction of musculoskeletal complaints and evidence of bone healing. Further follow-up was not possible, in view of the death of the patient. We believe that the patient's death was not directly related to the underlying pathology. However, it can be inferred that indirectly the clinically debilitated condition in which the patient presented may have contributed to the unfavorable outcome when confronted by severe sepsis.

Thus, we stress the need for greater recognition of the TIO as a cause of clinical bone pain, fractures, osteopenia and muscle weakness, superimposed on the characteristic biochemical profile with hypophosphatemia and relative hyperphosphaturia. Greater awareness of the disease will allow earlier diagnosis and ultimately a greater curative potential for patients afflicted with this syndrome.

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