

Oncogenic osteomalacia: a case report and review of the literature

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Oncogenic osteomalacia is a rare paraneoplastic syndrome characterized by severe hypophosphoremia due to renal phosphate wasting and osteomalacia clinically near to hereditary hypophosphoremic rickets. This disorder is induced by a benign tumor which belongs to the group of « phosphaturic mesenchymal tumor mixed connective tissue variant » secreting phosphaturic factors. We report the case of a 54-year old man who presented with diffuse bone pain and bilateral hip pain evolving for 3 years. Physical examination revealed a subcutaneous tumor of the left flank. A radiographic skeletal survey showed signs of osteomalacia with an overall « washed-out » appearance of the bone, cuneiform aspect of dorsolumbar vertebral bodies and bilateral fracture of femoral necks. Serum Fibroblast Growth Factor 23 concentration was high. The patient had total bilateral hips arthroplasty and surgical removal of the tumor of the flank was performed. There was rapid improvement and the laboratory values returned to normal.

Keywords: Oncogenic, Osteomalacia, Mesenchymal, Tumor, fibroblast growth factor.

Introduction

Oncogenic osteomalacia (OO) is a rare paraneoplastic syndrome characterized by severe hypophosphoremia due to renal phosphate wasting and osteomalacia clinically near to hereditary hypophosphoremic rickets. This disorder is induced by a benign tumor which belongs to the group of « phosphaturic mesenchymal tumor mixed connective tissue variant » (PMTMC) (1), secreting phosphaturic factors. Despite its frequent association with OO, PMTMC commonly presents clinical difficulties both in diagnosis and management. Measurement of Fibroblast Growth Factor 23 (FGF-23), a new identified clinical marker for oncogenic osteomalacia, has been recently of considerable importance for early diagnosis of this disorder.

We report here in a new case of oncogenic osteomalacia linked to a mesenchymal tumor of the flank compatible with the features of PMTMC.

Case Report

A 54-year old man, with no medical history, presented with diffuse bone pain and bilateral hip pain evolving for 3 years, having insidiously caused functional disability. The patient has been confined for a year because of permanent asthenia, weight loss. Physical examination revealed a painless mobile 3-centimeter diameter subcutaneous tumor of the left flank, primarily evoking lipoma. The patient was admitted for detailed investigations. Biology revealed low levels for serum inorganic phosphorus (0.52 mM; N: 0.85-1.45 mM), hyperphosphaturia (72 Mm / 24h; N: 12-40 Mm) and hypocalciuria (1.70 mM; N: 2.25-2.62 mM). A low level for serum 1,25-(OH) vitamin D (7 pM; N: 16-56 pM) was found, whereas serum levels of ionized calcium and 25(OH) vitamin D were normal. Serum and bone alkaline phosphatase were elevated (respectively 352 U/L; N: 38-115 and 87.1 ng/mL; N: 7.5-16), as well as serum intact PTH (95ng/mL; VN: 3-51 ng/mL). A radiographic skeletal survey showed signs of osteomalacia with an overall « washed-out » appearance of the bone, cuneiform aspect of dorsolumbar vertebral bodies and bilateral fracture of femoral necks Garden 4 (Figure1).

Diagnosis of hyperparathyroidism was first made but rapidly excluded since cervical ultrasonography didn't show parathyroid adenoma. Hypothesis of oncogenic osteomalacia was therefore evoked. Serum FGF-23 concentration was subsequently evaluated and was high estimated to 88 pg/mL (N < 40 pg/mL) confirming the suspected diagnosis.



Figure 1: Bilateral femoral necks fractures



Figure 2. Total bilateral hip arthroplasty

According to this, the patient had total bilateral hips arthroplasty 2 weeks a part (Figure 2) and surgical removal of the tumor of the flank was performed. Histological examination revealed an encapsulated tumor made of double adipic and vascular components including some hypervascularized areas and a well-defined central area with swelling, necrotic and haemorrhagic changes. There were neither mitoses nor tumoral necrosis favourable to malignancy. These histopathological features were compatible with the diagnosis of angiolipoma.

After surgery, the patient had multivitamin supplementation and intensive reeducation program. Outcome was favorable with correction of hypophosphatemia within 15 days following surgery. Clinically, he was able to walk using crutches and his pain improved.

Discussion

We reported here an anatomoclinical case of oncogenic osteomalacia in an old man due to a small, histologically benign tumor secreting high levels of FGF-23. In our patient, clinical features were typical with weakness, bone pain and spontaneous fractures. Biochemical abnormalities were also suggestive of oncogenic osteomalacia, namely hypophosphatemia and decreased serum 1-25-(OH)₂ vitamin D₃ levels.

Since the first description of oncogenic osteomalacia by Prader¹ in 1959, few cases have been reported in the literature². Diagnosis is often made in adult patients over 30 years³ as it is the case of our patient. This condition is problematic to recognise making the delay for diagnosis usually long ranging from few months to 19 years with an average delay of 2.5 years^{3,4}. Infact, the causative tumor may be small (varying from 1 to 15 cm), slow growing, and clinically unapparent. Moreover, these tumors may occur in many different locations, often making their detection difficult. Many histological types of these tumors have been reported^{2,5} such as haemangiopericytoma, giant cell tumor, osteoblastoma or angioliipoma such the case of our patient. Anyway, these tumors, usually benign, may also be malignant^{2,6}. Actually, cases of osteosarcoma, colon adenocarcinoma, breast or prostatic cancer have been described in association with oncogenic osteomalacia^{1,4,7,8,9}. Implicated tumors are usually located on the head and neck, preferentially in sinus and mandible. As in our patient, they also mainly affect bone and soft tissue^{3,7-11,15,16} especially in the lower extremities¹⁷.

They are histologically characterized by admixture of mesenchymatous cells and conjunctival tissue. Four histopathological contingents are suggestive for the diagnosis: spindle cells, osteoclast-like giant cells, cartilage-like matrix or metaplastic bone and haemangiopericytoma-like vascularization. Authors recognized that many of these tumors are quite distinctive but it was not until the study of Weidner and Santa Cruz¹⁴ that the term « phosphaturic mesenchymal tumor mixed connective tissue variant » was proposed to describe these particular lesions, a notion that was later emphasized by Folpe et al¹.

PMTMCT and other uncommon tumors causative of osteomalacia syndrome markedly over-express factors, causing impaired phosphocalcic and vitamin D metabolism¹⁸. Hypophosphatemia is due to excessive renal phosphate wasting induced by this new class of phosphaturic factors called phosphatonins; among them FGF-23 is considered as the new clinical marker for OO. Its action consists of inhibition of renal phosphate uptake and of 1-25 (OH) Vitamin D synthesis from 25 (OH) Vitamin D by inhibiting 1 alpha hydroxylase. That's why, we notice decreased serum levels of 1-25 (OH) Vitamin D even with hypophosphatemia¹⁹.

As previously reported^{20,21}, FGF-23 level was determined in our case by ELISA. In oncogenic osteomalacia, if the causative tumor can be located and completely removed, there is a rapid normalization of serum phosphate and remission of the disease. This evolution suggests that FGF-23 play a key role in this disease. In our patient, surgical removal of the flank tumor relieved symptoms with biochemical normalization within 15 days after surgery. However, after effects were noticed in our patient because of the delay of diagnosis. This to focus on the importance of early diagnosis of oncogenic osteomalacia to avoid sequelae.

Because surgical removal of the responsible tumor is the only satisfactory treatment, identification of the tumors is clinically essential. In our patient, diagnosis was quite easy since he had a clinically apparent tumor and typical biochemical features of oncogenic osteomalacia. Otherwise, diagnosis is usually hard in patients where tumor is difficult to locate and slow-growing. Recently, the use of PET/SCAN made it easier. However, FGF-23 measurement remains of considerable importance for facilitating early diagnosis of oncogenic osteomalacia, even if it is not specific of this condition since high levels are also found in X linked hypophosphatemia and autosomal dominant hypophosphatemic rickets. In the latter, the ground of pediatric patients with positive family history is suggestive.

Conclusion

We reported here a typical case of OO, a rare clinicopathologic entity linked to a mesenchymal tumor which overexpresses a hypophosphatemic factor, FGF-23, causing the major symptoms of the disease. Our patient experienced rapid remission after excision of the causative tumor. This is to highlight the importance of considering OO in the differential diagnosis of osteomalacia syndrome to avoid a delayed diagnosis and then sequelae.

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