CASE REPORT
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Oncogenic Osteomalacia: A Case Report and Literature Review

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ABSTRACT

Oncogenic Osteomalacia or Tumor Induced Osteomalacia (TIO) is a rare paraneoplasmatic syndrome characterized by multiple automatic pathological fractures as well as by severe hypophosphatemia. The etiology is not known, but its pathophysiology is associated with a very small mesenchymal tumor which is related to the Fibroblast Growth Factor 23 (FGF 23). Clinically the patient has numerous automatic fractures of the upper and lower limbs and of the spine, with bone and muscular pains. Hypophosphatemia, phosphaturia and increased alkaline phosphatase are the laboratory findings. Finding the tumor can be a major diagnostic challenge and the radical excision is the treatment of choice. A female patient, 47 years old, senior nurse, healthy in general, revealed a progressive weakness of the lower legs during the last two years, generalized myopathy and pathological fractures in pelvis, hips, humerus, sternum, clavicles, spine, radius and knees, symmetrical in both sides, left and right. Phosphorus and vitamin D were found very low and FGF 23 very high. Scan, CT and MRI were normal. The PET revealed a very small lesion in the base, under the tongue. The tumor was removed and the biopsy confirmed the phosphaturic mesenchymal tumor. Very soon the patient recovered, the fractures were united and today five years postoperatively, she is very well and free of the disease.

KEYWORDS: Tumor induced osteomalacia, hypophosphatemia, hyperphosphaturia, fibroblast growth factor.

Basic Knowledge and Related Literature

Tumor induced osteomalacia (TIO), is a very rare paraneoplasmatic syndrome. The prevalence of the disease is not known. It is estimated that more than 900 cases of TIO have been reported in the literature (1,2). In pathophysiology, TIO is characterized by severe hypophosphatemia and the most common cause of this is the phosphaturic disorders (1) which was demonstrated in mice (2). In humans this is confirmed by Miyachi et al (2). FGF23 was identified as strong phosphaturic substance (3) and was found in very high concentrations in TIO. FGF23 is also a regulatory hormone of 1,25 vitamin D and leads to a decrease concentration of this vitamin in the blood (3,4). Histopathologically, these tumors are usually very small, less than 1 cm, and of mesenchymal origin(2,5) with neoplasmatic cells. Mitotic activity of these cells is usually absent or very mild (2). While these tumors in vast majority are benign, malignancy and metastases can occur in some cases. (6) Infiltration of the surrounding tissue is typically present, so the surgical removal should be wide, in order to avoid persistence or recurrence.

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VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

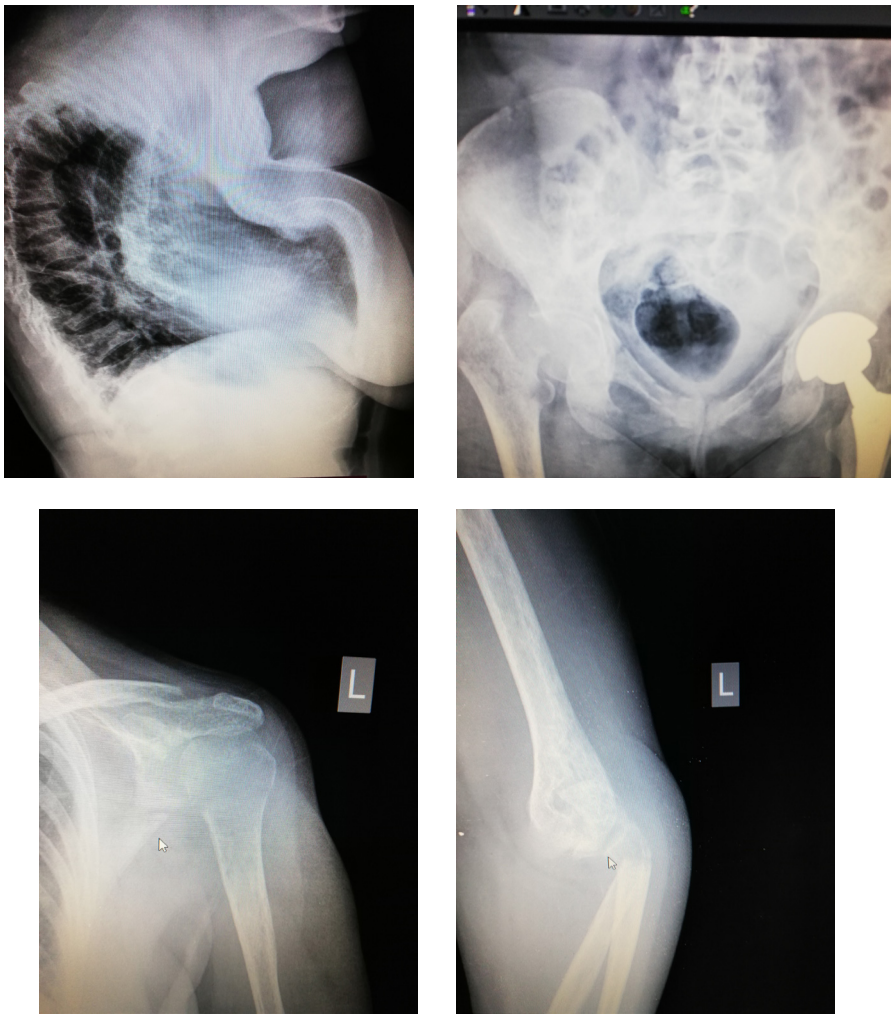

Figure 1. *Fractures of the sternum and spine (A), hip (B), clavicle and humerus (C), and elbow (D).*

The majority of the tumors is found in males (56%) and the mean age of diagnosis is the 45,3 years (2,4). Most tumors occur in the thigh and the femur (22,7%) and in craniofacial region (20,7%) and the rest in all the bones and soft tissues of the body. Very few cases were reported in organs such as the liver, the tongue, the thyroid and the lungs (7).

Clinically, common complaints are bone pain, muscle weakness and mainly the pathological automatic fractures, primary in vertebral bodies, ribs and femoral necks. In laboratory we have hypophosphatemia, caused by impaired renal phosphate, hyperphosphaturia, low levels of vitamin D, increased alkaline phosphatase and normal prices of the Calcium and Parathormone (PTH) except in the cases of secondary hyperparathyroidism. The very high prices of FGF23(1,2,6) confirm the diagnosis.

In differential diagnosis should always include renal Fanconi's syndrome as primary disorder or as complication of myeloma, amyloidosis or Sjogren's syndrome. It is also very useful the exclusion of genetic causes such as XLHR, ADHR and ARHR, by performing genetic tests (3,6,7).

The most challenging problem in this disease is to find the location of the tumor. This is due to the very small size and the fact that this tumor can be anywhere from the head to the toes in any bone or soft tissue, even subcutaneously and also has a very slow growing, through years. (7,8) Therefore we usually perform Total body Magnetic resonance (MRI), Computed tomography(CT), Scintigraphy(Tc99m) and positron emission(PET\CT) (8,9).

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

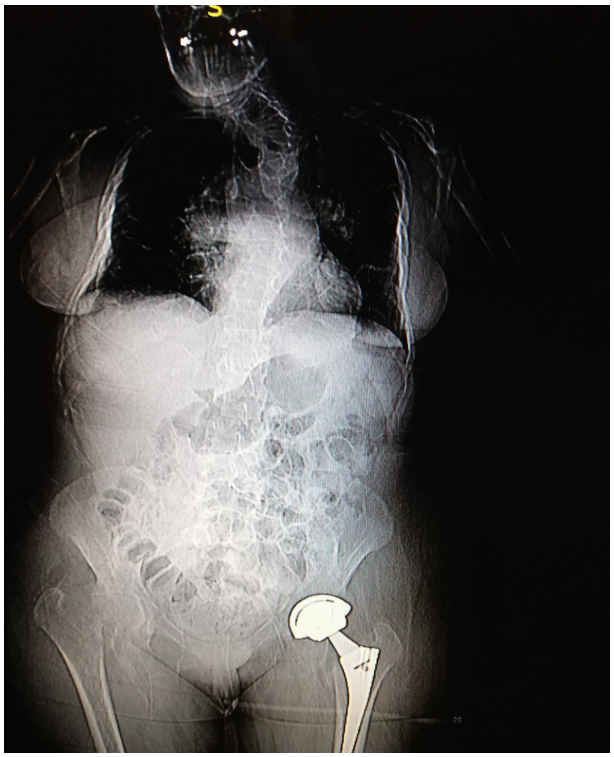

Figure 2. *Total body x-ray.*

The treatment of choice for TIO is the resection and removal of the tumor with a wide margin for complete tumor removal, as recurrences have been reported (10). After the removal of the tumor the patient feels much better immediately (within days or weeks). FGF23 disappears from the circulation rapidly, phosphorus and vitamin D return to the normal five days postoperative and bone healing starts immediately. In case of incomplete removal, radiotherapy can be used to avoid recurrence or metastasis. Radiofrequency ablation (RFA), octreotide and antibody for FGF23 have also been reported in combination with regular conservative treatment, such as the administration of phosphate and vitamin D, to have beneficial effect.

Case Report

A 47-year- old, female, senior nurse, healthy in general without any family or personal medical history, was complaining during the last two years of progressive weakness and musculoskeletal pain in the spine and limbs. The last author visited her at home and found a lady practically immobilized in bed, with severe weakness due to the generalizing myopathy and deformities, and in great pain in the limbs and the spine due to the fractures. The patient was admitted in the University Orthopaedic Department for further clinical and laboratory examination.

Clinical examination revealed scoliosis and kyphosis of the spine, weakness in muscles, deformities of the limbs and pain with palpation and movements. The neurological and endocrinological examination was normal and excluded parathyroid disease and myeloma.

Bone mineral density (DEXA) was normal (1000 mgr./cm2) and x-rays revealed osteomalacia with Looser's zones multiple fractures in different stage of union of the limbs, symmetrical in both sides. In detail there were fractures in clavicles, scapulae, humerus, radius, hips, knees, pelvis and also in sternum and at least in five vertebrae (20 fractures in total) (fig.1 and2).The first ultrasounds of thyroid, spleen, pancreas, kidneys ,liver and prostate were normal. The CTs, MRIs, the whole body scintigraphy with Indium 111 were normal as well in the beginning. All these investigations confirmed the fractures and osteomalacia but they could not reveal the cause of all these.

Laboratory examinations showed only low values of phosphorus in the blood (2,00 mg%, with normal values 2,5-4,9), very low vitamin D (3,0 gr/ml with normal values 18-65) and increased alkaline phosphatase (319,19 u/l with normal values 40-150u/l). All the other values were normal. The first possible diagnosis was Ongogenic Ostemalacia. The value of FGF23 was very high, 838(normal:<180pu/ml) and the diagnosis was confirmed. High doses of phosphorus and vit. D were administrated and the patient felt impressively well. The last MRI in the cervical spine revealed a small tumor (41x34x17 mm) beneath the right base of the tongue and eventually the PET/CT confirmed the diagnosis (fig.3). The tumor was removed from the second of authors on 26/4/2017 and the histological conclusion was 'Phosphaturic mesenchymal tumor '. The patient, even from the first week, had a very quick recovery from weakness and the levels of phosphorus and vitamin D came back to normal values. The progress of fractures' union was also impressive.

This case report is presented for the following reasons: 1) The Tumor Induced Osteomalacia (TIO) is very rare. Less than 1000 cases have been reported all over the world. 2) The appearance in the tongue is

VOLUME 74 | ISSUE 2 | APRIL - JUNE 2023

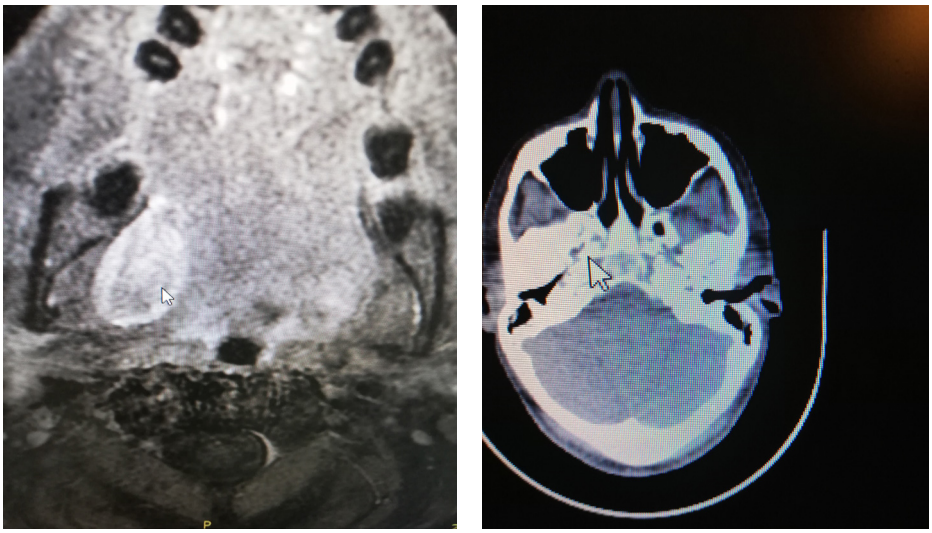

Figure 3.*The TIO in PET (A) and MRI scan (B).*

much rarer. 3) TIO is always a diagnostic and therapeutic challenge. In half of the reported cases, the final diagnosis and the finding of the tumor were delayed for some years. In addition, the removal of this tumor in some cases was very difficult and was not reachable. 4) In our case we had many pathological fractures, more than twenty. These fractures in the limbs were symmetrical. 5) The recovery after the tumor's excision was impressive and today five years from removal the patient is free from the disease.

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