Oncogenic osteomalacia

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Summary

Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome characterized biochemically by hypophosphatemia, excessive urinary phosphate excretion, low 1,25-dihydroxyvitamin D levels, and clinically by osteomalacia, pseudofractures, bone pain, fatigue, and muscle weakness. TIO can occur in patients with a variety of benign mesenchimal tumors (hemangiopericitomas, fibromas, angiosarcomas, etc.) and the disease is invariably curable with the removal of the tumor, indicating that it has humoral basis. Phosphate wasting and the defect in vitamin D synthesis are caused by a humoral factor produced by tumors, initially termed phosphatonin, and recently identified as fibroblast growth factor-23 (FGF-23) although other substances as secreted frizzled-related protein 4 (SFRP4) and matrix extracellular phospho-glycoprotein (MEPE) can be involved in pathophysiology of osteomalacia. In contrast with more common forms of osteomalacia, patients with TIO have normal serum calcium, normal serum 25-hydroxy-vitamin D and normal intact serum parathyroid hormone. On the other hand TIO is biochemically indistinguishable from several inherited forms of hypophosphatemic rickets as X-linked hypophosphatemia (XLH) and autosomical dominant hypophosphatemic rickets (ADHR). The definitive diagnosis of TIO is established by identification of the causative tumor and remission of the syndrome after complete tumor resection. Recently a few cases in which ^{111}In-pentetreotide scintigraphy visualized the tumor have been reported and also positron emission tomography using F-18-fluorodeoxyglucose showed encouraging results. When the suspected tumour cannot be located, periodical follow-up with conventional imaging is indicated with special attention directed to craniofacial locations and extremities because they are the more common localization for tumour. In conclusion in patients with TIO resection of a tumour is the treatment of choice; if the tumour cannot be found or if the tumour is unresectable for its location, chronic administration of phosphate and calcitriol is indicated.

KEY WORDS: oncogenic osteomalacia, hypophosphoremia, fractures, octreotide scintigraphy.

Introduction

Osteomalacia is a metabolic bone disorder characterized by reduced mineralization and increase in osteoid thickness. This disorder typically occurs in adults, due to different conditions impairing matrix mineralization. Its major symptoms are diffuse bone pain, muscle weakness and bone fractures with minimal trauma. When occurs in children, it is associated with a failure or delay in the mineralization of endochondral new bone formation at the growth plates, causing gait disturbances, growth retardation, and skeletal deformities, and it is called rickets.
Histologically patients with osteomalacia present an abundance of unmineralized matrix, sometimes to the extent that whole trabeculae appeared to be composed of only osteoid (Fig. 1). This will be depicted by quantitative histomorphometry as increases in osteoid volume, surface and thickness. However, hyperosteoidoisis could be observed in other bone diseases with a high turnover as hyperparathyroid states. The osteomalacic nature of the hyperosteoidosis is being demonstrated by defective mineralization, irregularity of mineralization fronts, high number of osteoid lamellae, broad single tetracycline fluorescent labels or no label at all, in contrast to the normal double tetracycline fluorescent labels. These qualitative observations have to be supported by the unequivocal changes in quantitative histomorphometry: decreases in a double and single tetracycline labeled surface and in mineral apposition rate as well as prolongation of mineralization lag

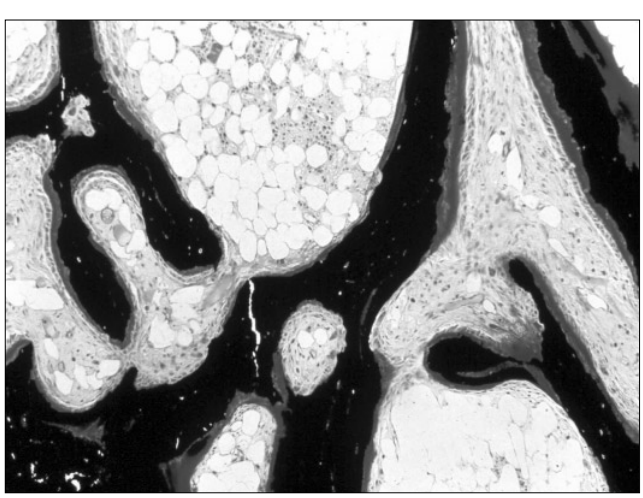

Figure 1 - Osteomalacia. Excessive accumulation of osteoid and increased width of osteoid seams. Undecalcified section of human iliac bone (Von Kossa stain).

time (1).
Many cases of osteomalacia are related to vitamin D deficiency (Tab. I). This condition, also named nutritional osteomalacia, can be due to either estrinsic or intrinsic vitamin D deficiency. The former is mainly related to low dietary intake or reduced sunlight exposure, while intrinsic vitamin D deficiency is caused by an impaired intestinal absorption of vitamin D. Osteomalacia may also occur due to impaired vitamin D metabolism. In rare circumstances, rickets may be due to hereditary disorders of vitamin D metabolism (1-alfa-hydroxylase deficiency, causing type I vitamin D dependent rickets) or vitamin D resistance due to impaired vitamin D receptors (causing type II vitamin D dependent rickets). Finally, different conditions, such as phosphate depletion, renal tubular acidosis, or treatment with fluorides and etidronate, may cause vitamin D independent syndromes leading to osteomalacia.
Oncogenic osteomalacia or tumor-induced osteomalacia (TIO) is an acquired disorder of isolated renal phosphate wasting that is associated with tumors, often arising from a mesenchymal tissue. It is a rare disorder with at least 120 cases reported in the literature (2). The first case was described by McCance, in 1947 (3), even thought the causal relationship between malignancy and osteomalacia was not recognized until 1959 (4).

Pathophysiology

TIO is characterized by hypophosphatemia due to inhibition of renal phosphorus reabsorption associated with a vitamin D synthetic defect that blocks the compensatory rise in calcitriol stimulated by the hypophosphatemia. Phosphate wasting and the defect in vitamin D synthesis are caused by a humoral factor produced by mesenchymal tumors, termed phosphatonin. Recently this substance has been identified as a 32-kD peptide belonging to the Fibroblast Growth Factor family, FGF-23.
Other causes of selective renal wasting of phosphate are: 1) X-linked hypophosphataemia (XLH); 2) autosomal dominant hypophosphataemic rickets (ADHR); 3) hereditary hypophosphataemic rickets with hypercalciuria (HHRH).
TIO is usually characterized by generalized pain and muscle weakness. Otherwise, TIO mimics the clinical phenotype of XLH or ADHR. In patients with TIO, a family history of hypophosphatemia and bone disorders is absent and onset and severity of symptoms are more acute than in the other hypophosphatemic syndromes. XLH and ADHR typically present in childhood, although ADHR can exhibit a variable and delayed age of onset. On the other hand patients with TIO exhibit symptoms as weakness, pain, and fractures that are more severe, with rapid progression to disability. However, also patients with adult-onset ADHR may present severe bone pain and weakness. Stress fractures are a prominent feature of osteomalacic states while lower-extremity deformity and short stature are characteristic of XLH and ADHR. HHRH replicates many features of the phenotype of XLH and ADHR but it is distinguished by an appropriate increase of calcitriol and hypercalciuria (5, 6).
Shimada et al. (7) first identified FGF-23 as the humoral factor produced by tumors and causing oncogenic osteomalacia. When injected into mice FGF-23 produced mild phosphaturia and hypophosphatemia. Moreover FGF-23 is high expressed in mesenchymal tumors causing tumor-induced osteomalacia and it is barely detectable in normal tissues such as liver, thymus, heart, lymph nodes, brain (7, 8). FGF-23 exerts its activity at the proximal renal tubule by the inhibition of tubular reabsorption of phosphate and the downregulation of 25-hydroxy-vitaminD-1-hydroxylase, resulting in hypophosphatemia and osteomalacia (9).
FGF-23 is also central in the pathogenesis of ADHR. Missense mutations in 1 of 2 arginine residues at positions 176 or 179 have been identified in affected members of ADHR families. These mutated arginine residues prevent the degradation of FGF-23, resulting in prolonged and/or enhanced FGF-23 action (10-14).
Additional evidence suggests that FGF-23 may also be the key in the pathogenesis of XLH caused by mutations in the *PHEX* gene (phosphate-regulating gene with homologies to endopeptidase on X chromosome), which encodes an endopeptidase. Speculation about how loss of endopeptidase activity results in phosphate wasting has led to the hypothesis that FGF-23 is a substrate for *PHEX* and that failure to cleave FGF-23 prolongs or enhances its activity. Although there is disagreement in the literature, *PHEX* is thought to, either directly (10, 15) or indirectly (16, 17), regulate FGF-23. Thus, FGF-23 plays a central role in the disorders of renal phosphate wasting. In TIO, tumors produce FGF-23 which exerts its activity at the proximal renal tubule; in ADHR, FGF-23 bears mutations that enhance its bio-

Table I - Etiopathogenetic classification of osteomalacia.

Vitamin D deficiency	**Phosphate depletion**
Estrinsic deficiency	Low dietary intake
Reduced sunlight exposure	Drugs
Low dietary intake	Renal tubular acidosis
Intrinsic deficiency	Selective renal wasting of phosphate
Impaired intestinal absorption	X-linked hypophosphataemia (XLH)
Gastrectomy	Autosomal dominant hypophosphataemic rickets (ADHR)
Celiac disease	Hereditary hypophosphataemic rickets with hypercalciuria (HHRH)
Intestinal by-pass	**Tumour-induced ostemalacia (TIO)**
Hepato-biliary disease	**Vitamin D metabolism deficiency and normal phosphate**
Chronic pancreatic deficiency	Mineralization inhibitor
Impaired vitamin D metabolism	Drugs
Deficiency of 25-OHD	Acidosis
Anticonvulsivant drugs	Deficiency of matrix mineralization
Hepatic chronic disease	Fibrogenesis imperfecta ossium
Deficiency of 1,25-$(OH)_2$D	Alkaline phosphatase disorders
Renal chronic insufficiency	Ipophosphatasia
Type I vitamin D dependent ipophospatemic rickets	

logical activity and render it resistant to proteolytic cleavage; in XLH, mutated *PHEX* directly or indirectly leads to the accumulation of FGF-23 in the circulation and exerts its phosphaturic activity at the renal proximal tubule (Fig. 2). In some patients with polyostotic fibrous dysplasia who exhibit renal phosphate wasting, serum FGF-23 can be elevated, correlating with the severity of skeletal involvement (18). However, FGF-23 is not the only factor secreted by tumors that affects renal phosphate handling and bone mineralization (19-22). Other compelling phosphatonin candidates have been identified as secreted frizzled-related protein 4 (SFRP4) and matrix extracellular phospho-glycoprotein (*MEPE*). Genetic studies of tumors inducing osteomalacia showed a high level of expression of the RNA for SFRP4 (23) and an evaluation of the biological effects of SFRP4 on opossum kidney epithelial cells evidenced a reduction in phosphate reabsorption. Furthermore, infusion of SFRP4 to rats diminished phosphate reabsorption without increasing the urinary AMPc levels; this effect persisted in parathyroidectomized rats, indicating that it was independent from PTH (24). The *MEPE* is a recently identified gene with a high level of transcription in tumor induced osteomalacia (25). It encodes an extracellular matrix protein, also called *MEPE*. In mice, *MEPE* expression occurs chiefly in the osteoblasts and is more marked during bone mineralization phases. The *MEPE* expression was reduced by 1,25-OH-D3 in HYP mice, a model of XLH characterized by a high level of *MEPE* expression (26) and decreased *MEPE* hydrolysis related to a *PHEX* gene mutation responsible for increased *MEPE* activity has been suggested (27). In cultures of human proximal tubule epithelium, *MEPE* inhibited phosphate reabsorption. In animals, intraperitoneal *MEPE* injection induced hypophosphatemia and hyperphosphaturia in a dose dependent manner. Finally, an in vitro study showed dose dependent inhibition by *MEPE* of murine osteoblastic mineralization in the presence of BMP2 (22). However data on these new forms of phosphatonin come from a limited number of studies and require confirmation.

The tumors associated with TIO are of mesenchymal origin in the large majority of patients (Tab. II). The occurrence of osteomalacia in patients with widespread fibrous dysplasia of bone (28, 29), neurofibromatosis (30, 31) and linear nevus sebaceous syndrome (33) could also be tumor induced. However, in one case of fibrous dysplasia (29) and linear nevus sebaceous syndrome (32) removal of the abnormal bone or skin lesions respectively resulted in biochemical and radiographic improvement. Oncogenic osteomalacia has also been associated with osteosarcomas (33-35), angiosarcomas (36), chondrosarcomas (37), and malignant neurinoma (38) as well as nonmesenchymal carcinomas of the prostate (39, 40) and lung (41), chronic lymphocytic leukemia, and multiple myeloma (42).

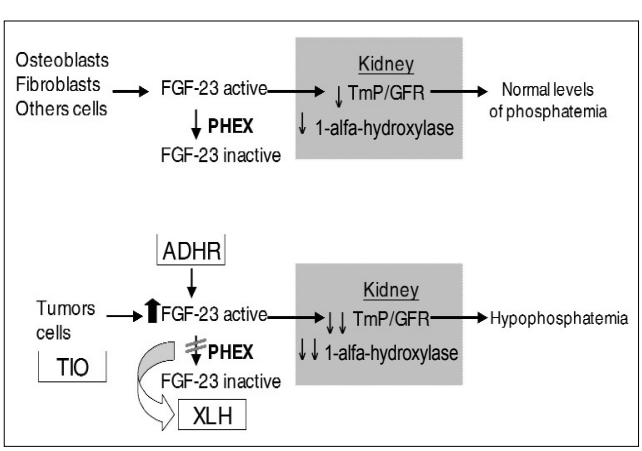

Figure 2 - Hypotetical model of interaction between FGF-23 and *PHEX*.

Table II - Tumors frequently associated to osteomalacia.

Tumor type
> 10%
Hemangiopericytoma
5-10%
Mesenchymal tumor
Non-ossifying fibroma
Prostatic carcinoma
1-5%
Angiolipoma
Epidermal naevi
Malignant chondroblastoma
Giant cell chondroma
Giant cell granuloma
Giant cell tumor
Hemangioma
Hemangioendothelioma
Cavernous hemangioma
Ossifying mesenchymal tumor
Ossifying fibroma
Fibroangioma
Osteoblastoma
Benign osteoblastoma
Polyostotic fibrous dysplasia
Primary bone tumor
Sebaceous naevi
Sclerosing hemangioma
Synovial tumor
< 1%
Benign connective tissue tumor
Brown tumor
Degenerated osteoid
Diffuse giant cell tumor
Extraskeletal chondroma
Mesenchymal chondrosarcoma
Atypical chondroma
Giant cell fibrous malignat histiocytoma
Hemangiofibroma
Mesenchymal spindle cell tumor
Mesenchymoma
Mixed mesenchymal tumor
Vascular mesenchymoma
Myelomatosis
Neurinoma
Neuroma
Malignant neuroma
Oat cell carcinoma
Odontogenic fibroma
Fibrosarcoma
Low grade fibrosarcoma
Fibrous xanthoma
Osteochondroblastoma
Osteosarcoma
Paraganglioma
Sarcoma
Small cell carcinoma
Transitional cell carcinoma
Vascular tumor

There are also reported cases of benign tumors becoming malignant over time.
The mesenchymal tumors associated with this kind of osteomalacia have been variably described as sclerosing angioma, benign angiofibroma, hemangiopericytoma, chondrosarcoma, primitive mesenchymal tumor, soft-parts chondroma-like tumor, and giant-cell tumor of bone. Weidner and Cruz (31) established that the polymorphous mesenchymal tumors can be subdivided histologically into four distinct morphologic patterns: (a) primitive-appearing, mixed connective tissue tumors; (b) osteoblastoma-like tumors; (c) non-ossifying fibroma-like tumors; and (d) ossifying fibroma-like tumors. The most common of these, the mixed connective tissue variant, occurs in soft tissue, behaves in a benign fashion, and is characterized by variable numbers of primitive appearing stromal cells growing in poorly defined sheets and punctuated by clusters of osteoclast-like giant cells. Vascularity also is prominent, but in less-vascular areas, poorly developed cartilage or foci of osteoid or bone are commonly present. The cartilage-like areas sometimes exhibit considerable dystrophic calcification. The tumors are usually small, slow-growing, difficult to locate, and present in obscure areas. In this regard, many of the reported lesions have been located in a relatively inaccessible area within bone, such as within the femur or tibia, the nasopharynx, mandible, or a sinus. Alternatively, small lesions have been found in the popliteal region, the groin, the suprapatellar area, and in the brain. FGF-23 is abundantly expressed in these tumors (10, 43).

Diagnostic evaluation

Clinical and biochemical characteristic

Oncogenic osteomalacia affects both sexes around the age of 40 years. It may affect children and adolescents in 20% of cases. In most patients, clinical signs appear from several months to many years before the discovery of the tumor. In some cases, the presence of a neoplastic mass was noted long before the onset of skeletal disease.
The clinical symptoms of TIO are non specific and often lead to an erroneous diagnosis. Bone pain has been reported in the majority of patients and it may be associated with tenderness, weakness and muscle pain (44-46). Pain in osteomalacia is dull and poorly localized but clearly felt in the bones rather than in the joints (1, 47). It is often persistent, made worse by weight-bearing and contraction of locally attached muscles. The pain is usually symmetrical, beginning in the low back, later spreading to the pelvis and hips, upper thighs, upper back, and ribs. Lateral compression of the ribs and posterior compression of the sternum are useful maneuvers to elicit pain. Muscles of the proximal limb girdles, especially the lower, are often weak, the severity varying from a slight abnormality to severe disability verging on complete paralysis. Specific symptoms include difficult in rising from a chair or walking up or down stairs without using the arms (1). Abnormal gait is the most frequent clinical manifestation of osteomalacia, and it can be the result of either pain or weakness, but usually both contribute. The combination of trunk oscillation, short steps, and wide track contributes the classic penguin or duck-like waddling gait of advanced osteomalacia (48). Children with TIO also display rachitic features including gait disturbances, growth retardation, and skeletal deformities.
The constant biochemical markers of TIO are severe hypophosphatemia, ranging from 0.7 to 2.4 mg/dl. Hyperphosphaturia, increased serum alkaline phosphatase and low plasma concentration of 1.25-dihydroxy-vitamin D are also frequent (1).
The serum calcium is usually normal but mild hypocalcemia has been described. The serum PTH levels are usually within normal limits, but have been found low or high in some cases (44-46). Circulating levels of 25-hydroxy-vitamin D are normal and there are not glycosuria and aminoaciduria (49). Hypophosphatemic osteomalacia can be a rare but important complication of multiple myeloma. In these cases, the pathophysiology of the phosphate renal wasting is notably different from oncogenic osteomalacia and is due to light-chain nephropathy, resulting in proximal tubular dysfunction (50).
In cases in whom inherited hypophosphatemic rickets must be excluded, genetic tests for mutations of the *PHEX* gene (defective in XLH) and the FGF-23 gene (defective in ADHR) are useful (51).
Recently a serum assays has been developed to determine if circulating concentrations of FGF-23 were elevated in TIO patients. The first reported assay was an 'intact' FGF-23 ELISA assay that used confirmation-specific monoclonal antibodies to N- and to C-terminal portions of FGF-23 (52). By this method, FGF-23 can be detected in normal individuals with a mean circulating concentration of approximately 30 pg/ml without correlation with age. The single TIO patient tested in this study had a serum FGF-23 concentration approximately nine-fold above controls before tumor resection. After tumor removal, circulating FGF-23 concentrations decreased within 30 min, and serum phosphorus improved within 6 h (52). The rapid fall of FGF-23 post-tumor resection and rapid rise in serum phosphorus concentrations was also confirmed by findings in subsequent TIO cases (53-55). In a study with a large number of controls and TIO patients, the C-terminal ELISA was used to assess the role of FGF-23 in TIO (53). This study confirmed that FGF-23 can be detected in the circulation of normal individuals, and demonstrated that the mean FGF-23 was greater than 10-fold in the TIO patients tested compared to controls. Interestingly, in a manner similar to XLH patients, some TIO patients had serum concentrations within the normal range (56).

Imaging

In osteomalacia conventional radiography can reveal a marked decrease of bone density and multiple pseudo-fractures. Technetium-99m bone scintigraphy demonstrates diffuse skeletal uptake, referred to as a "superscan", and focal uptake at sites of fractures. Reduced bone density can be determinated also by dual-energy X-ray absorptiometry (DEXA) but it is impossible to distinguish the underlying aetiology of the osteomalacia with these techniques.
Repeated attempts to identify the tumour by physical examination and conventional imaging studies are frequently unrewarding, so that surgical treatment cannot be performed. Recently, a few cases in which ^{111}In-pentetreotide scintigraphy visualized the tumor were reported (57-60). Indeed, "in vitro" studies showed that many mesenchymal tumors express somatostatin receptors (61) and also lesions smaller than 1 cm may be visible if receptor density is high, producing strong radioisotope uptake with a sharp contrast between the tumour and the background noise (Fig. 3). However, phosphaturic syndromes are not always related to oncogenic osteomalacia, so that a negative somatostatin receptor scan is not necessarily a false-negative result. Because identification and surgical removal of the tumor is extremely beneficial to the patient and in view of the high failure rate of conventional imaging techniques to identify these small tumours, it seems reasonable to recommend ^{111}In-pentetreotide scintigraphy as the initial imaging study in the assessment of patients with suspected oncogenic osteomalacia (60). However it is important to underline that not all oncogenic osteomalacia tumours express somatostatin receptors, or can

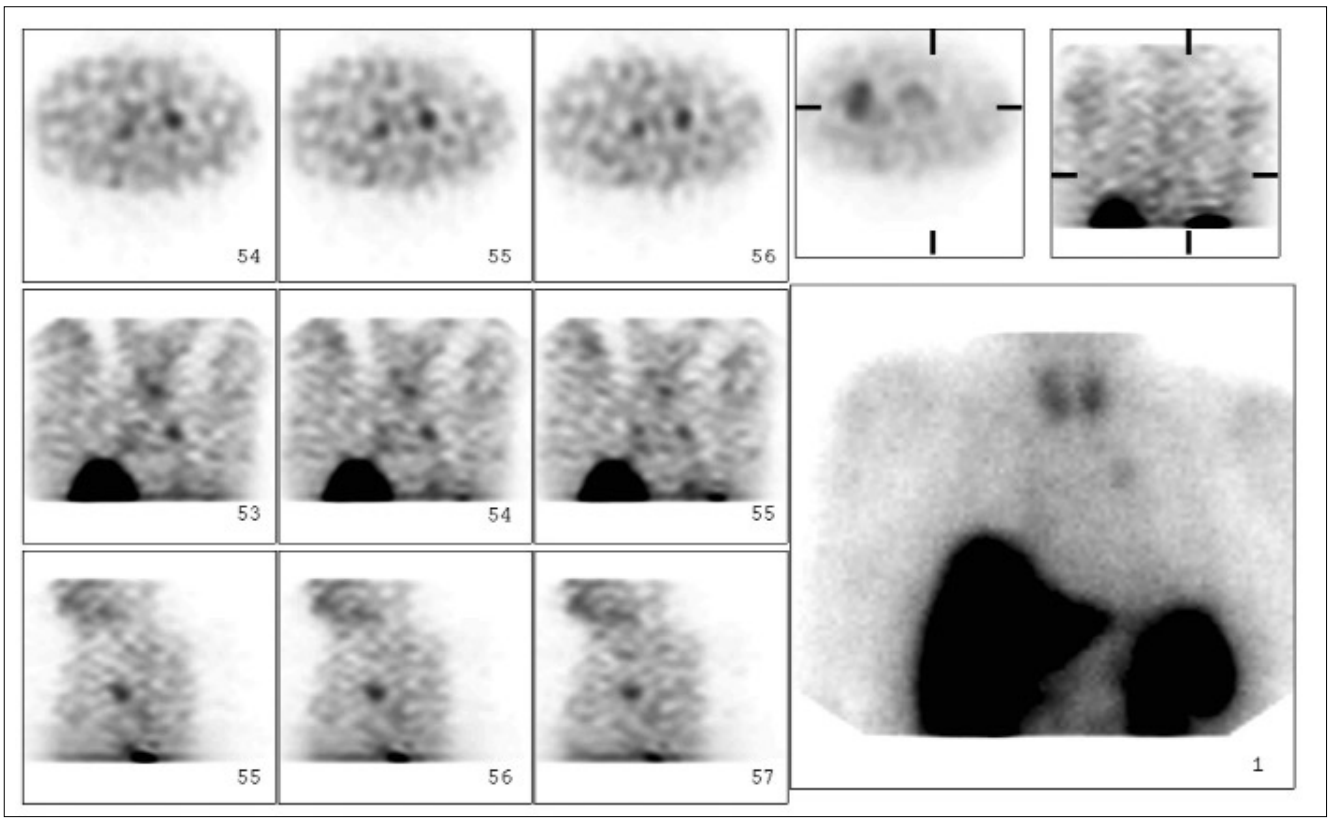

Figure 3 - Tumour of the lung causing TIO localized by ^{111}In-octreotide scintigraphy.

be detected with octreotide scanning.
Positron emission tomography (PET) using F-18-fluoro-deoxyglucose (FDG) is the most important nuclear medicine procedure applied to oncology for diagnosis and staging (62). The clinical impact of 18F-FDG PET has been reported for many different tumor types. In an extensive review of the 18F-FDG PET literature, the overall sensitivity and specificity was estimated to be 84% and 86%, respectively, and the results from 18F-FDG PET changed the management in approximately one third of the patients (63). Tumor imaging with 18F-FDG is based on the fact that malignant tumors with high metabolic rates take up greater amounts of glucose and 18F-FDG than surrounding tissues. Not all malignant tissues have avidity for 18F-FDG. Some types of cancer tissues with low malignant potential, such as carcinoid tumor, bronchoalveolar cancer, and mucinous adenocarcinoma, use 18F-FDG at the same rate as normal surrounding tissues, leading to failure in identifying these kind of cancers (64-67). In a case-report 18F-FDG PET was used to confirm the diagnosis of oncogenic osteomalacia: a search was conducted for a mesenchymal tumor by total body CT, MRI, and ^{111}-indium octreotide scintigraphy with negative results. PET images demonstrated an isolated focus in the mouth region. Selective MRI confirmed the presence of a solid mass between the 37th and 38th tooth (68). When we use CT or MRI particular attention must make to craniofacial regions and extremities because these are the most frequent localizations of these kind of tumours (Fig. 4).

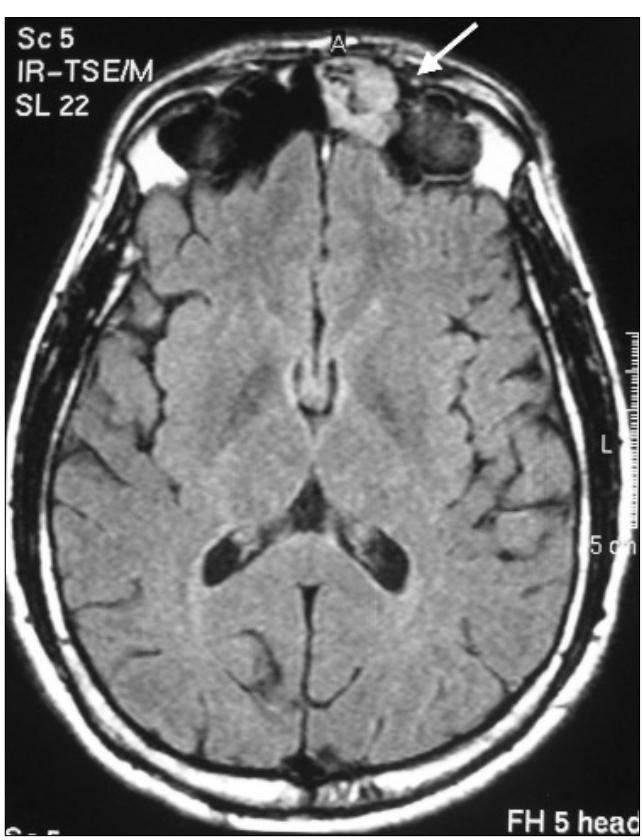

Figure 4 - Head CT scan showing an ossyfyng fibroma-like tumour of frontal sinus.

Treatment

In patients with TIO resection of the tumour is the treatment of choice (Fig. 5) (69). If the tumour cannot be found or if the tu-

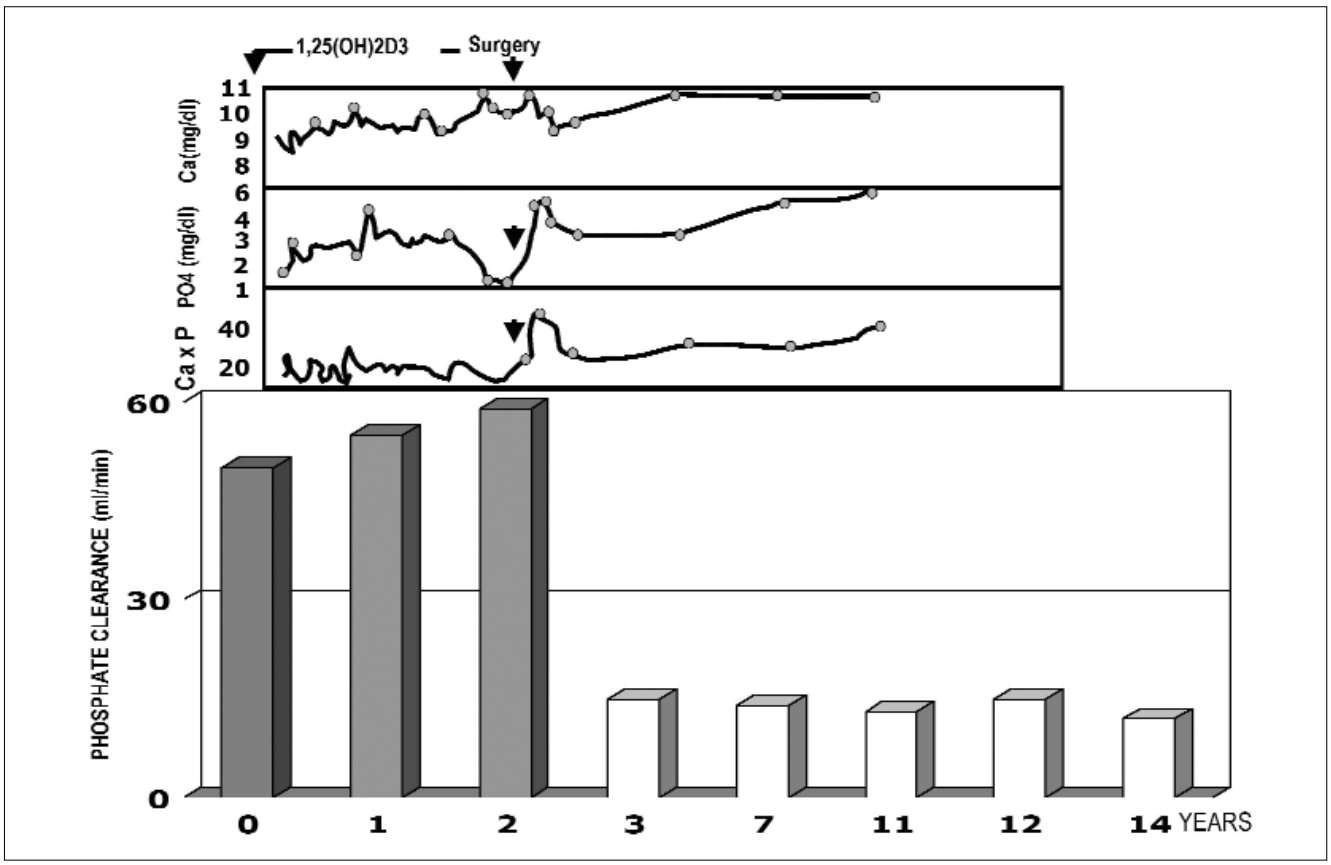

Figure 5 - Serum calcium and phosphorus levels before and after surgical removal of haemangiopericytoma of maxilla causing TIO.

mour is unresectable because of its location, chronic administration of phosphate and calcitriol is indicated. Some patients can be made asymptomatic and maintain a good quality of life on these two medications. Regular monitoring of biochemistry (every 3 months) ensures compliance and safety. It is preferable to initiate oral treatment with phosphate, equivalent to 3 g/day elementary phosphorus, in divided doses, and adjust the dose according to gastrointestinal tolerance and biochemical response. If oral phosphate is not tolerated because of diarrhea, long-term intravenous infusion is an option. Because the solution is hyperosmolar it must be administered by central catheter and carries the risk of catheter-related infection. The healing process can be expedited by using larger doses of calcitriol initially up to 5 mcg/day to achieve supraphysiological concentrations of the hormone. As the serum alkaline phosphatase falls to normal it is prudent to reduce the dose of calcitriol to 1-2 mcg/day. If the osteomalacia is accompanied by a normal alkaline phosphatase it is better to monitor the response to 1 mcg doses of calcitriol initially, only increasing the dose if there is no clinical improvement. Long-term monitoring is necessary to ensure that there is no evidence of developing hyperparathyroidism. Indeed tertiary hyperparathyroidism requiring parathyroidectomy may develop if too much phosphate or too little calcitriol is used; hence the need for regular follow-up, including PTH measurements (70). In those cases deemed to be idiopathic, careful reexamination for small tumours should be undertaken; but where a patient is easily managed medically, exhaustive reinvestigations looking for small benign lesions are not necessary.

There is also some experience with the administration of octreotide (57). In a case, treatment with subcutaneous octreotide, 50 to 100 µg 3 times a day, resulted in correction of hypophosphatemia, improvement in phosphaturia, and reduction of alkaline phosphatase (57). However, in 2 other patients, despite 8 weeks of treatment with subcutaneous octreotide, up to 200 µg 3 times daily, serum levels of phosphorus and calcitriol failed to increase, and tubular reabsorption of phosphate remained depressed (60). Given the limited experience with octreotide treatment in TIO, this therapy should be reserved for the most severe cases that are refractory to current medical therapy (51).

Conclusions

TIO is a rare disorder that presents with muscle weakness, bone pain, and osteomalacia. Because the symptoms are often non-specific, the measurement of serum phosphorus can be very useful in patients with bone pain of unclear origin, muscle weakness and fractures. Tumor-induced osteomalacia is usually caused by benign mesenchimal tumours and cure can be achieved by complete resection of these tumours. From this point of view, the location of the tumour is of paramount importance.

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