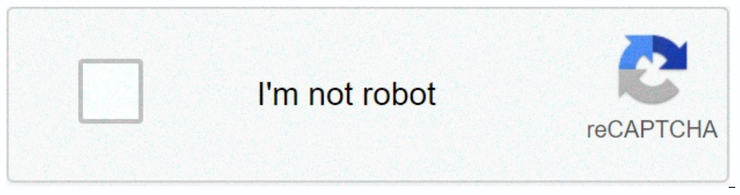

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Oncogenic osteomalacia pdf

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In addition, experimental evidence supports the role of cancer products that affect the transport of renal tubular cell phosphate and the activity of 1α-hydroxylase [6-9]. Currently, the term oncogenic hypophosphotomic osteomalament (OHO) is applied in this group. OHO was first recognised more than 40 years ago [10]. However, despite musculoskeletal symptomology, it is rarely reported in rheumatological literature [11-14]. In addition, most cases were published as one case history shortly after patients appeared to be cured by surgery [3, 4]. Diagnosis and management issues that have rarely been addressed include (i) the extent and methods of finding such tumours; (ii) risk of relapse after surgery; (iii) optimal drug treatment in both early stages and long-term control; and (iv) the risk of other long-term complications. In addition, repeated reports of delays in diagnosis of up to 19 years [4] indicate that the condition is poorly recognised. That is why we are briefly presenting the case history of four patients who have been monitored for up to 23 years to illustrate each of these problems. Reports of the case The patient, a 48-year-old Caucasian woman, was first referred to a metabolic unit in 1975, 12 years after the initial onset of extensive musculoskeletal pain. She originally underwent an intensive neurological examination in 1962 without a diagnosis and within 3 years became a home. Osteomalalys was finally diagnosed in 1965 when she broke both hands while lifting her newborn baby, and X-rays revealed eight separate sites of the previous fracture. She was treated daily with calciferol 50,000 IU and within 3 years her symptoms had disappeared. In the 1970s, cystic 4-inch swelling overlaying the left shoulder blade was removed, histology was reported as cystic lymph angioma. She then discontinued calciferol, but in 1973 relapsed with widespread skeletal pain, weakness and fatigue. On the recommendation, she had proximal myopathy, she was unable to grow out of a chair. A small, solid, non-commercial, non-automatic perizaular mass was detected. The general review was otherwise notable. showed plasma phosphorus 0,46 - 0,61 mmol/l (normal range 0,8 -1,4); serum alkaline phosphatase (ALP) was 10.0-11.4 King-Armstrong (KA) units in the normal range (4-12). Other normal findings included full blood count (FBC), erythrocyte sedimentation rate (ESR), liver enzymes, feces fat excretion, renal and bone biochemistry including calcium hormone and parathyroid gist (PTH), creatine phosphokinase (CPK), blood glucose and serum protein electrophoresis. There was no rheumatoid factor, anti-nuclear antibody, Bence Jones urinary protein, glycosurrium or aminoaciduria. X-ray graphs showed osteopenia, a healing left distal ulnár and right subtrochanteric fractures, and typical pseudophaturia in two metacarpal bones. An undecalized biopsy of transiliac bones revealed pronounced osteomalacia. Histological examination of periscapulary matter, which was incompletely removed under general anaesthetic, showed properties similar to the original biopsy (which was restored and reassessed), although it was consistent with the diagnosis of sclerosing hemangioma. Two days after the removal of the matter, fasting serum phosphorus increased to 0.94 mmol/l. She was treated with 25-hydroxycholecalciferol (calcidiol) 1 mg per day (kindly donated by Upjohn Co., Kalamazoo, MI, USA) during a metabolic balance study (unpublished results) and for 1 week was able to rise unattended from the chair. Within 1 month, she felt healed. Vitamin D2 1 mg per day has been replaced and 1.5 g of elemental phosphorus per day (as Sandoz t.d.s.) added to the treatment regimen. Phosphate and later vitamin D2 were stopped, but within 6 months its symptoms returned and plasma phosphorus fell. Phosphate and calcidiol have been re-adjusted, but no residual tumour has been identified clinically or by computed tomography (CT) from head to abdomen. Long-term treatment with 1α-hydroxycholecalciferol (alfacalcidol, 1-alpha) and phosphate has been resumed. She remained generally well for 21 years, although her symptoms of the mesculoskeletal system and biochemistry varied slightly until the dose of alphacalcidol was increased from 2 to 3 µg per day in 1987. In 1996, after 1 year of borderline normal levels, mild hypercalcaemia was detected and within 3 months it was acutely accepted elsewhere with pyonephosis, staghorn renal calculus, serum calcium of 2,77 mmol/l and glomerular filtration of 27 ml/min. The medication was stopped and she underwent a nephectomy. Subsequently, normal PTH levels were demonstrated. Phosphate and alphacalcidol recovered after developing symptoms of osteomalamate associated with hypophosphataemia 3 months later. Her condition remains under control. Patient 2 In 1979, a 60-year-old woman was referred to a metabolic unit with a 5-year-old bilateral knife and diffuse left leg pain, for which she saw four doctors. The previous year she underwent a hip discectomy for sciacia disease with little subsequent relief. She then developed bilateral pain in her hip, shoulder and ribs with progressive weakness and difficulty Her diet was good, although she reported 3kg of weight loss. The examination revealed pronounced proximal myopathy and generalized bony tenderness, but otherwise it was unusual. There was no obvious tumor. Tests showed low plasma phosphorus

(0.50-0.61 mmol/l) and ALP units 13-19 KA (normal range 4-12), but other blood and urine tests were normal, as in patient 1. X-ray scans showed generalised osteopenia with multiple pseudopharmaceuticals of the ribs and femur. An undecalized, transiliac bone biopsy showed severe osteomalacia. Diagnosis of acquired hypophosphatamic osteomalalysis was made and initially treated with 10 µg alfacalcidol, 8 g Ossopan daily and Sandoz q.d.s. phosphate. Her symptoms improved within days. Within a month, they had largely been resolved. A metabolic balance study has previously been reported confirming the need for phosphate supplements during this phase [15]. Sandoz phosphate was then reduced to t.d.s., alfacalcidol to 2 µg per day and later to 1 µg per day and remained well with normofophaemia for 2 years. She then began relapse with associated hypophosphaemia (0.66-0.82 mmol/l). In 1992, she underwent a CT scan from head to pelvis and weight was shown in the etmidoid sinus. Histology of the carved tumor revealed hemangiopericytoma. All drugs were then stopped and for 4 years her clinical condition, although characterized by occasional musculoskeletal symptoms, remained stable with normal serum phosphorus and ALP. In 1986, an relapse and bone biopsy again confirmed osteomalatic: it was again hypophosphatomy (0.53 mmol/l), but the CT scan showed no apparent tumor. Treatment was resumed, this time with calcitriol 0.5 µg per day and Sandoz phosphate. She then became depressed and anxious (though not hypercalcaemic). In 1998, her intestinal habit changed. Colon cancer was diagnosed elsewhere, and although resection of the intestine appeared initially successful, she died of metastatic disease in 1989. In 1991, a 3,59-year-old Caucasian woman was referred to a metabolic unit after a pathological fracture of the distal tibia and a 10-year history of progressive loss of height, back pain and diffuse limb, which she saw many specialists. She suffered a supracondylar fracture of the elbow after falling 3 years before the referral. At the time she was taking vitamin D 800 IU daily for several months without benefit. She was unable to walk and bitterly complained of diffuse pain and weakness in her limbs. The examination revealed pronounced thorax kyphosis, sensitivity of the chest wall and proximal muscle weakness. Abnormal tests were serum phosphorus 0.4 mmol/l (normal range 0.8-1.2), ALP 1247 IU/l (normal range 100-280) and serum 1.25 (OH)2D 11.2-13.7 pg/ml (normal range 25-45). All other blood and urine tests, such as patient 1, were normal. X-ray sictures revealed osteopenia, bilateral pseudophaturia of the pubic rami, affected by a fracture of the left femur neck and a rough collapse of the vertebrae (Fig. Bone density lumbar (L1–L4) (BD) by double X-ray absorption (DXA) was 1.90 standard deviations (s.d.) below the age of mean and technetion-99m-labelled MDP (99mTc-MDP) bone scans showed focal areas of tracer accumulation in the axial and appendicular skeletons. Undecalized biopsy of transiliac bones showed significant osteomalacia. A CT scan from head to pelvis did not reveal the tumor. Initially, calcitriol 6 µg per day was treated with phosphates and calcium supplements for more than 3 months, during which time its pain and fatigue improved steadily; however, the circulating level of 1.25(OH)2D did not increase above 25.4 pg/ml. Eventually, she admitted with embarrassment the swelling of the vuvy, which she had for years. The weight of the soft tissues, which gynecologists considered to be Bartholin's cyst, was cut out and histologically confirmed as a hemangiopericytome. The excitement was considered incomplete at the time. However, despite reducing the dose of calcitriol to 4 µg per day, serum increased to 1.25(OH)2D to 43.8 pg/ml and serum phosphate increased to 1.56 mmol/l. The relationship between its various biochemical indices was briefly reported at this time [16]. Calcitriol was further reduced and eventually stopped 5 months after surgery. Within a month, however, the ALP increased and phosphate and 1.25 (OH)2D dropped to 0.7 mmol/l and 15 pg/ml. Treatment with phosphate and calcitriol was re-established and remained in order after 8 years of follow-up, although affected by kyphosis, for maintenance doses of Sandoz t.d.s. phosphate and calcitriol 0.5 µg per day. Attempts to further reduce the dose of phosphate and calcitriol were associated with a decrease in serum phosphate and 1.25(OH)2D. She refused further surgery on Perine. Opened in a new tabDownload slideMultiple thoragen fracture in a 59-year-old woman with a 10-year history consistent with the diagnosis of osteomalacy, eventually diagnosed as oncogenic hypophosphateic osteomalacy associated with vulval hemangiopericytoma (patient 3). In 1997, a 4,61-year-old Iranian man was referred to a metabolic unit with a 5-year history of gradual worsening of extensive pain and weakness. In Iran in 1995, it turned out to have typical radiographic features of Paget's disease in the right femur, which was confirmed by a bone biopsy, after which he came to Britain for professional orthopedic and rheumatological consultation elsewhere. Paget's disease of the right femur and also L4 has been confirmed; However, disseminated malignancy was also suspect because of its generally poor condition, weakness and widespread musculoskeletal pain associated with multiple truncal, rib and appendicular skeletal abnormalities reported at the 99mTc-MDP (methylene dipphosphonate) scan (Fig. 2). Tests including serum protein electrophoresis, urine analysis for Bence Jones protein, liver function, prostate-specific antigen, abdominal ultrasound and CT scan were normal. Bone marrow and iliak biopsy (decalcified) have not shown malignancies. Nevertheless, it was concluded that the most likely similar diagnosis was metastatic carcinoma from an unknown primary tumour and was treated with neopa opiate analgesics and calcitonin for bone pain. He returned to Iran at the end of 1996. However, his weakness, mobility and pain slowly deteriorated. He then returned to Britain and was reliant on our unit in January 1997. Due to pain and weakness, he became completely addicted to his family to complete all his domestic activities. He was a stove man, had severe proximal myopathy, was unable to rise from his chair and could only mobilize with crutches. He had extensive vitiligo. The examination was otherwise notable and no tumor was found. A review of all medical records prior to referral revealed increased ALP and persistent hypophosphaemia (0.39-0.69 mmol/l). Abnormal tests in our unit were plasma phosphorus 0.36 mmol/l (normal range 0.7-1.5), ALP 345 IU/l (normal range 35-115), plasma 2247 nmol/l (normal range 20-195) and 1.25 (OH)2D <1 pmol/l (normal range 25-150). Apart from evidence of Paget's right femur disease and L4 and general osteophobia, there were no other radiological symptoms, especially no pseudopharmaceuticals. DXA lumbar spine BD (L1–L4) was 3.23 years lower than age-aligned mean. An uncalcified transiliac bone biopsy showed severe osteomalasia with 100% coverage of t trabecular surfaces with broad osteoid tissue. Normal tests included FBC, ESR, renal and bone biochemistry including plasma calcium and PTH, liver function, blood glucose and CPK. The search for malignancies, including examination of stools for occult blood, abdominal ultrasound and CT scans of the pharynx and paranasal sinuses, was negative. A diagnosis of acquired hypophosphatemic osteomalalation was made. It was treated with 4 µg calcitriol per day (reduced after 4 days to 3 µg), sandoz t.d.s. phosphate and initially 1500 mg of calcium per day in divided doses. A marked improvement in muscle strength occurred within 3 weeks and was associated with normalization of its plasma phosphorus. Within 6 weeks he was able to walk without using a cane. Plasma phosphorus and calcium stabilized within the normal range on 3 tablets of Sandoz phosphate and 2 µg of calcitriol per day. After 4 months, his pain practically resolved and became freely mobile; However, he still had low back pain and elevated ALP, presumed secondary paget disease. Before returning to Iran, he was treated with intravenous pamidronáte for long-term medications. After 2 year, a maintenance dose of calcitriol of 0.75 µg per day remains well. All PTH and 1.25(OH)2D measurements in our hands have been carefully validated with respect to normal ranges and reproducibility [17]. Open in new tabDownload slideWhole-points 99mTc-MDP images in hypophosphate osteomalalysis (patient 4). The scan shows multiple areas of discrete indicator localization. Areas that are radiographically in line with Paget's diseases are represented by a tracer catcher in the right femur and L4. Discussion Diagnosis of acquired hypophosphatemic osteomalalysis requires recognition of the typical clinical and radiological properties of osteomalalysis in relation to hypophosphaemia [5]. Other conditions associated with hypophosphaemia should be excluded (Table 1). The diagnosis of OHO occurred in the first three patients after the detection of the tumor, which after removal led to an improvement in symptoms and biochemical indices. Diagnosis of OHO remains possible in the fourth patient. Although acquired hypophosphotomic osteomalacity is a rare disease, these four cases illustrate a completely disproportionate toll, which its lack of recognition accurate. Table 1.Biochemical findings in the main conditions obtained, characterised by hypophosphataemia and musculoskeletal symptoms (from reference 34, abbreviated) Status Plasma indices Urinary indices Nutritional osteomalaisation Calcium ♥ or low/normal calcium ♥ 25 hydroxyvitamin D ♥phosphate normald 1,25 dihydroxyvitamin D ♥, normal or ↑b PTH ↑ ALP ↑c Oncogenic osteomalaisation Calcium normal Calcium normal 25 hydroxyvitamin D normal phosphate normald 1.25 dihydroxyvitamin D ♥ Occasional PTH normal or ↑ aminoacid ria ALP ↑c Acidic forms of osteomalaciate Calcium normal or ♥ Calcium normal or ↑ 25 hydroxyvitamin D normal phosphate normald 1,25 dihydroxyvitamin D normal or ♥ Aminoaciduria P NORMAL OR ↑ ALP ↑c Primary a hyperpathyroidism Calcium ↑ Normalg calcium or ↑ 25 hydroxyvitamin D normal phosphate normald 1,25 dihydroxyvitamin D normal or ↑ PTH ↑ ALP normal or ↑f Humoral hypercalcaemia calcium ↑ Calcium ↑ malignancy (PTHrPh) 25 hydroxyvitamin D normal phosphate normald 1.25 dihydroxyvitamin D normal or ♥ PTH normal or ♥ ALP normal Delay diagnosis of OHO and tumor search Despite more than 100 cases of acquired hypophosphate osteomalacy and OHO in the literature [13], diagnosis remains easily missed. Common to all our cases were consultations with a number of doctors, delayed correct diagnosis (3-12 years) and prolonged morbidity. In the worst case scenario, as in patient 4, and as previously reported [18], patients may have misguided neoplasia with secondary skeletal metastases. In the fourth case, the presence of Paget's disease diverted attention from the possibility of osteomalacy, although clearly the significance of hypophosphaemia was unfousted and the possibility of osteomalalation was not increased in the radiologist's bone scan report. After recognition of hypophosphate osteomalasis, another question is the extent to which an associated tumor should be sought. As the first three cases show, tumors are often small, difficult to localize and in unclear areas. This is in line with most other cases [3, 13]. In two of our patients, the tumors were superficial (subcutaneous), although sufficiently easily noticeable. Tumours may pre-catch the onset of osteomalalysis or diagnosis of hypophosphate osteomalasia [19]. The question remains, as regards patient 4, whether and what kind of examination should be carried out in the next search for the tumor. If the patient is unaware of any odd lump, and if a thorough clinical examination fails to identify one, then imaging studies should be conducted. Optimal imaging modality is unknown, but since most tumours are in the extremity and many bones [13], bone scintigraphy may be useful [20], although it will be difficult to interpret in the presence of osteomalacia and/or other bone diseases. As tumours have a significant vascular fermentation in approximately 50% of cases [13], scintigraphy with radiopharmaceuticals having a significant blood pool phase and angiography should also be considered [21, 22]. We would also recommend, like others [3], that investigating head and neck can be rewarding. There are no data comparing CT performance and magnetic resonance imaging in the search for tumours. Management of acquired hypophosphatamic osteomalalysis and OHO Acquired hypophosphatapic osteomalacy will always respond to large doses of vitamin D or its strong derivatives and phosphate supplements [2,5]. Although it has been stated that the presence of a suitable tumour prevents the complete disappearance of osteomalalysis [4], it is clear from this report that patients can only be in good health for years on the basis of medical treatment. While finding a tumor is important because its complete resection routinely effects the drug [3-5], it is also clear from our report that relapse can be just as common if patients are monitored long enough. In addition, these tumors are not encapsulated, and complete resection can be problematic. Either way, it is clear that large doses of calcitriol or alphacalcidol and phosphate supplements quickly alleviate symptoms in the early stages [3, 4, 23] and speed up recovery to see if the tumor has been successfully resected. Metabolic balance studies have shown an additional effect of calcium supplements during the first 4 to 6 months of healing [2]. Our experience suggests that only when patients have recovered clinically should calcitriol be discontinued to determine whether the medicine has actually occurred. Relapse of osteomalacis While reported medicinal products indicate that treatment is safely discontinued after clinical and biochemical retouching following tumour reseciation, it is clear from this report that the frequency of relapse has been insufficiently emphasised in the literature. Incomplete resection, as with our first and third patients, is one obvious reason. Multicentre tumours are another option [20, 24, 25]. The cause of relapse in our second patient, 4 years after discontinuation of treatment, is unclear, since the CT scan did not identify the recurrence of the tumor at the original site. Her terminal colon cancer is a possible candidate and the unofficial reference was to hypophosphaemia patients with metastatic disease [3,4]. In general, long-term follow-up appears to be a prudent measure. Long-term pharmacological management All four of these cases illustrate that pharmacological treatment may be necessary in the long term. Experience from current cases, other cases in our experience (T.C.B. Stamp, unpublished findings) and those in the literature suggest that patients may be maintained at 0.5–1 µg calcitriol or 2–3 µg of alphacalcidol together with the supplement 1500 mg phosphorus per day. We are not aware of any studies that indicate optimal careful timing of supplementation. The importance of regular kidney monitoring to prevent progressive calcification is all too well illustrated in the first case, although purely infectious aetiology cannot be excluded. Finally, it was reported that tertiary hyperpathyroidism occurs in 5 % of OHO cases [4]. This may be an underestimation as it was observed in two of the original series of nine patients with acquired hypophosphaemia [5]. Its aetiology has been discussed [4, 14, 26, 27, although this may simply be a complication of long-term phosphate supplementation, calcium levels and induction of parathyroid hyperplasia, as in hypophosphatic rickets associated with X [28]. Tumours in OHO Tumours occurring in OHO have been variously described as sclerosing angioma, benign angiofibre, hemangiopericytoma, chondrosarcoma, primitive mesenchymal tumour and giant bone cell tumour [3,4]. The most common morphological pattern is characterized by stromal cells growing in poorly defined leaves, osteoclast cells, cartilage islands and pronounced vascular activity [29]. Acquired hypophosphotomic osteomalasia may also be associated with various cancers of epidermal and endodermal origin [30], multiple myeloma and chronic lymphocytic leukaemia [31]. It is also associated with fibrous bone dysplasia [32] and neurofibromatosis [3,33]. The exact way tumours are associated with biochemical and renal OHO abnormalities is unknown. There is some evidence to suggest that in many cases the effects on the handling of renal phosphates and 1.25(OH)2D production may be due to humoral factor (or factors) caused by tumours acting on renal tubular cells. First, tumor extracts can provoke phosphoric activity when infused into dogs [6]; secondly, a tumour transplanted into atypical naked mice may induce hypophosphaemia and phosphaturia [7, 8]; and thirdly, tumour extracts have been shown to inhibit the activity of 25-hydroxyvitamin D-1α-hydroxylase in renal tubular cell cultures [7]. Recently, two candidate proteins (~56-58 kDa) have been identified in tumour media derived from cultured tumour cells from an OHO patient, which according to the authors may be associated with a change in the co-transport of sodium-dependent phosphates and 1α-hydroxylase activity in renal cells, as reported in vitro [9]. Concluding remarks These cases confirm that the slow recognition of hypofosfatomických hypofosfatomických and OHO among physicians continue to lead to unnecessary and long-term morbidity. Cases emphasize that osteomalasis can before discovering a tumor and illustrate that the location and nature of tumors and their complete resection is often difficult to confirm. Importantly, even after seemingly complete resection of the tumor and recovery of the patient, relapses may occur and long-term pharmacological treatment may be necessary. Finally, serious complications of long-term treatment may develop. Therefore, we would advocate maintaining a high OHO suspected index in patients with persistent unexplained pain and weakness associated with biochemical functions suggestive of hypophosphomic osteomalacia (Table 1). Assiduous follow-ups with tumor recurrence supervision, biochemical monitoring and regular renal examinations are important for all patients in whom OHO has either been diagnosed or is likely to be diagnosed. Correspondence with: G. Clunie, Department of Rheumatology, Ipswich NHS Trust, Heath Rd, Ipswich IP4 5PD, United Kingdom. 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