Case Report

A Man with Osteoblastic Metastasis and Hypocalcaemia

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ABSTRACT

We report a case of an 80-year-old man with osteoblastic metastases from advanced carcinoma of the prostate presenting with a grand mal seizure resulting from severe hypocalcaemia. He had low serum phosphate and ionised calcium levels, elevated serum skeletal alkaline phosphatase and intact parathormone levels. ^{99m}Tc radioisotope bone scan revealed a “super bone scan” suggestive of osteomalacia. The serum 1, 25-dihydroxycholecalciferol level was unexpectedly elevated. The biochemical abnormalities persisted despite high dose calcium replacement, but improved with supraphysiological doses of 1,25 $(OH)_2$ vitamin D_3 (RocaltrolT) therapy. We hypothesise that the hypocalcaemia in this patient was due to vitamin D resistance secondary to a humoral factor secreted by the tumour.

Keywords: hypocalcaemia, hypophosphatemia, oncogenic osteomalacia

INTRODUCTION

Hypocalcaemia is an uncommon paraneoplastic manifestation. Tumour associated osteomalacia as a cause of hypocalcaemia was first described by McCance[1] who reported resolution of osteomalacia in a 15-year-old girl after removal of a degenerating osteoid tumour from her femur. Since then, approximately 60 cases have been described wherein a tumour has been clearly documented as the cause of osteomalacia[2].

CASE REPORT

An 80-year-old Chinese man admitted for hypertensive heart failure was found to have extensive sclerotic metastases on plain radiography of the lumbosacral spine. Per rectal examination revealed an asymptomatic hard nodule over the right lobe of the prostate and serum prostate specific antigen was grossly elevated at 910 eg/L (NR = 0 - 40).

Shortly after his admission, he had an episode of grand mal seizure. Computerised axial tomogram (CAT) study of the brain did not reveal any space occupying lesion or cerebral metastasis. His serum biochemical results were as shown in Table I. There was marked hypocalcaemia (with a low ionised calcium level) which was the probable cause of the seizure. Intact PTH (iPTH) was markedly elevated in response to the hypocalcaemia ie. secondary hyperparathyroidism. Moreover, there was hypophosphatemia and raised serum alkaline phosphatase, and heat treatment fractionation suggested a predominant skeletal source. Serum magnesium level was (low) normal. ^{99m}Tc bone scan was described as “super bone scan” consistent with metabolic bone disorder such as osteomalacia (Fig 1). The 25-hydroxycholecalciferol level was normal but the 1, 25-dihydroxycholecalciferol level was elevated in this patient. Furthermore, undecalcified skeletal biopsy only showed metastatic cells but did not reveal classical changes of osteomalacia. The hypocalcaemia was not corrected with aggressive calcium supplement but improved with supraphysiological doses (0.5 eg/day) of 1, 25 -dihydroxycholecalciferol.

DISCUSSION

While hypercalcaemia is a commonly encountered paraneoplastic manifestation, hypocalcaemia is rare. A malignant neoplasm with skeletal deposits resulting in hypocalcaemia and osteomalacia would appear to be an intriguing paradox.

Approximately 60 cases have been described wherein a tumour has been clearly documented as the cause of osteomalacia[2]. Most of these tumours were benign and the patients usually presented with classical symptoms of osteomalacia namely bone pain, proximal weakness and even genu valgus which resolved with resection of the neoplasia. The neoplasm usually presented itself before the onset of symptomatic osteomalacia. Nevertheless, one recent report described a 24-year-old patient who first presented with clinical signs and symptoms of osteomalacia and a search for occult neoplasm led to the discovery of an asymptomatic mesenchymal lung tumour[3]. The implicated neoplasia are so varied that there was initial difficulty in classifying them histologically. The literature suggested that oncogenic osteomalacia is usually associated with two main groups of neoplasia (Table II). Interestingly, non-neoplastic lesions such as Paget’s disease of the bone, Albright’s syndrome and fibrous dysplasia have also been found to be associated with osteomalacia.

The exact pathogenic mechanism of oncogenic osteomalacia has been a point of contention since its initial description. The early investigators including Randall and Lireman[4], Tommaso and Tucci[5] as well as Smallridge et al[6] proposed the increased skeletal avidity (“hungry bone”, “calcium sink”) theory in which the rapid skeletal accretion of calcium by the osteoblastic metastases was believed to be responsible for the hypocalcaemia. In recent years, the tumour associated humoral factor theory has gained the attention of many investigators. The development of this theory can be traced back to more than three decades ago when the term oncogenic osteomalacia was first coined by Drezner and Feinglos[7] to describe a patient with giant cell tumour of the bone and osteomalacia. In this report, the patient presented with the syndrome of hypophosphatemia, decreased renal tubular absorption of phosphate, hyperaminoaciduria, normal 25-hydroxycholecalciferol but reduced 1, 25-dihydroxycholecalciferol and osteomalacia

proven on skeletal biopsy. These abnormalities resolved with 1, 25-dihydroxycholecalciferol. Hence, it was proposed that a tumour-induced inhibition of 25-hydroxycholecalciferol-la-hydroxylase activity was responsible for the observed biochemical abnormalities. This mysterious tumour derived factor was not identified till 1988 when Miyauchi et al[8] demonstrated the occurrence of hyperphosphaturic osteomalacia in athymic nude mice after transplantation of tumour tissue from a patient with hemangiopericytoma induced osteomalacia. Extract from this tumour exhibited non-cAMP dependent inhibition of 25-hydroxycholecalciferol-la-hydroxylase activity in renal tubular cells. He further characterised the humoral factor to be an interleukin-1 like peptide (heat labile, trypsin resistant and lipid soluble). A recent report by Wilkins et al[9] described a patient with oncogenic osteomalacia from an infratemporal fossa paraganglioma which was used to establish a cell culture line. The conditioned medium obtained from the cell culture inhibited phosphate reabsorption by the kidney's tubular cells providing collaborative evidence for a yet unidentified hormone that produces phosphaturia. A less well established pathogenic mechanism suggested in 1972 by Olefsky et al[10] was the presence of a tumour-secreted vitamin D antagonist which induced a state of vitamin D resistance resulting in the syndrome of osteomalacia. Fig 1 depicts the unified theory on the current understanding of the pathogenic mechanism of oncogenic osteomalacia.

Our patient exhibited three unusual features. Firstly, a catastrophic presentation such as a grand mal seizure due to severe hypocalcaemia from oncogenic osteomalacia has not been previously reported. Secondly, in contrast to previous case reports, our patient's serum 1, 25-dihydroxycholecalciferol level was elevated suggesting a state of vitamin D resistance ie. relative rather than absolute vitamin D deficiency. Moreover, aggressive calcium supplementation alone did not correct the hypocalcaemia until a supraphysiological dose of 1, 25-dihydroxycholecalciferol (0.5 eg/day) was administered. This provides additional support to our hypothesis that vitamin D resistance was the cause of the hypocalcaemia. Alternatively, the elevated serum 1, 25-dihydroxycholecalciferol may just be a response to the high parathormone level. However, the later explanation appears to contradict the popular view of the presence of a 25-hydroxycholecalciferol-la-hydroxylase inhibiting humoral factor. Thirdly, although the biochemical picture was consistent with osteomalacia, the undecalcified skeletal biopsy did not reveal osteomalacic changes probably because of the rapidly progressive nature of the underlying malignancy leaving insufficient time for classical histological changes to occur in the bone.

In conclusion, the pathogenesis of oncogenic osteomalacia is likely to be complex and perhaps heterogeneous in different malignancies. Our report provides new insight into the pathogenetic mechanism of oncogenic osteomalacia in that tumour associated vitamin D resistance may be important.

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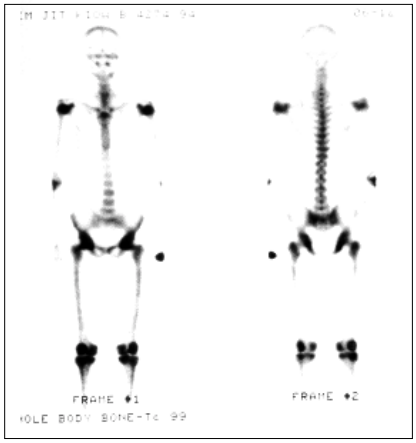

Fig 1 - Bone scan of the patient showing generalised intense tracer uptake.

Table I - Serum biochemical and hormonal profile of the patient

Investigations	Results
Serum calcium (2.10 - 2.60 mmol/L/(Albumin) (36 - 45 g/dL)	
Through	1.71/(25)
After treatment	2.12/(28)
Serum phosphate (0.70 - 1.40 mmol/L)	
Through	0.54
After treatment	0.99
Peak serum alkaline phosphatase (50 - 107 IU/L)	1511
Ionised calcium (1.14 - 1.32 mmol/L)	0.77
Serum magnesium (0.7 - 0.95 mmol/L)	0.74
Parathormone level (4.7 - 48.5 pmol/L)	430
Serum creatinine (41 - 141 emol/L)	75
25 hydroxycholecalciferol (15 - 80 ng/mL)	
Pre-treatment	27
1, 25 dihydroxycholecalciferol (15 - 60 pg/mL)	
Pre-treatment	150

Table II - Two main groups of neoplasia associated with oncogenic osteomalacia

Main group	Sub-type	Remark
Mesenchymal tumour (Weidner, 1991)	Phosphaturic mesenchymal tumour of a) Mixed connective tissue variant b) Osteoblastoma like variant	This group of neoplasia is usually benign and mostly of osseous and soft tissue origin
Osteoblastic metastasis	Carcinoma of the prostate[11] Carcinoma of the breast[12] Oat cell bronchogenic carcinoma[13]	

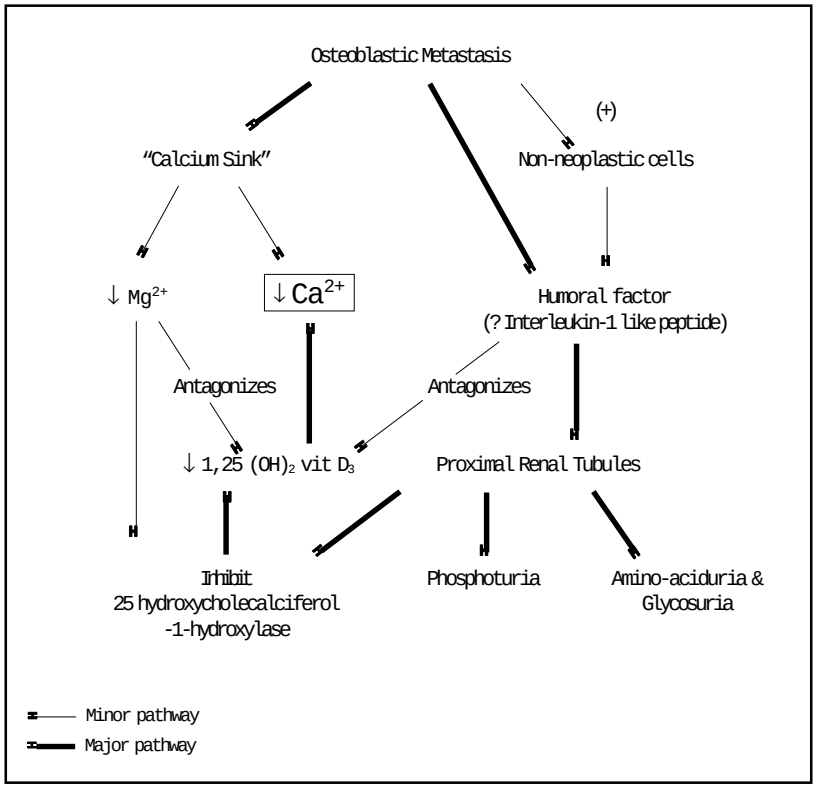

Fig 2 - The pathophysiology of oncogenic osteomalacia.