Vitamin D Resistant Hypophosphatemic Osteomalacia Associated with Osteosarcoma of the Mandible: Report of a Case

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A case of vitamin D resistant hypophosphatemic osteomalacia associated with osteosarcoma of the mandible is presented. The patient complained of lumbar, knee and foot pain and muscle weakness of two years' duration. Serum phosphorus was 1.0-1.6 mg/dl, tubular reabsorption of phosphorus was 47 to 58%, TmPO_4/GFR was 0.7-1.2 mg/dl. Aminoaciduria was noted. Bone biopsy confirmed the diagnosis of osteomalacia. He partially responded to the treatment with $1\alpha(\text{OH})\text{D}_3$ and sodium phosphate. After removal of sarcoma of the mandible, symptoms remitted and pertinent laboratory data became normal except serum alkaline phosphatase for more than one year without treatment. It is suggested that an impaired response of the tubule and bone to active vitamin D_3 , caused in some way by the osteosarcoma might be one of the causes of osteomalacia in this case.

Key Words: Vitamin D resistant osteomalacia, Osteosarcoma, Mandible

Since 1947, 19 cases of vitamin D resistant osteomalacia associated with mesenchymal tumor have been reported¹⁾²⁾ and referred to as tumor rickets³⁾ or oncogenic osteomalacia⁴⁾. The pathogenesis of this syndrome is still obscure, although Drezner and Feinglos⁴⁾ suggested 1, 25-dihydroxyvitamin D_3 [$1, 25(\text{OH})_2\text{D}_3$] deficiency as the cause. Recently Fukumoto et al¹⁾ suggested that the tumor might primarily induce proximal tubular impairment and this, in turn, causes excessive urinary loss of phosphorus and the defective formation of $1, 25(\text{OH})_2\text{D}_3$. We present a case of vitamin D resistant osteomalacia associated with osteosarcoma of the mandible, whose clinical symptoms and pertinent laboratory data became normal, except serum alkaline phosphatase level, after the removal of osteosarcoma.

CASE REPORT

A 29 year old man was admitted to Kanazawa University hospital in February 1979 with complaints of lumbar, knee and foot pain and muscle weakness of two years' duration. During the last six months, the complaints had progressed to total confinement in bed. He had lost approximately 3 cm in height during this period. There was no family history of bone disease, renal disease or endocrine gland tumor.

Physical examination disclosed tenderness over the ribs, sternum, second to fourth lumbar spine, extremities and mandible. His jaw, chest and extremities had no deformity or muscle atrophy. No neurological deficit was noted, but he could not walk and had difficulty in standing up due to

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pain and muscle weakness. His heart, lung and abdomen revealed no significant abnormalities. Lymphadenopathy was not noted.

Red blood cell count, hemoglobin, leucocyte count and differential, and platelets were all within normal limits. Serum calcium was 4.3–4.7 mEq/L (normal 4.2–5.7), and phosphorus was 1.0–1.6 mg/dl (normal 2.7–4.4). The tubular reabsorption of phosphorus (TRP) ranged from 47 to 58% (normal 82–95). The tubular maximum for the reabsorption of phosphate normalized to glomerular filtration rate ($TmPO_4/GFR$) was calculated by the method of Bijvoet⁶⁾ and was 0.7–1.2 mg/dl (normal 2.5–4.2). Other electrolytes, blood urea nitrogen, serum creatinine, serum uric acid and plasma proteins were all normal. Serum protein electrophoresis revealed no abnormalities and immunoglobulin assay was within normal limits. An oral glucose tolerance test was normal. Urinalysis showed neither proteinuria nor glycosuria. Determination of 24-hour amino acid excretion revealed increases in lysine, i.e. 147.4 mg/dl (normal 7–48) and glycine, i.e. 280.5 mg/day (normal 68–199). Excretion

of other amino acids were within normal range. Urinary β_2 -microglobulin was 164.5 μ g/day (normal 30–140 μ g/day). Ammonium chloride loading test was normal, the urine pH decreased to 5.05. Urinary concentrating ability and renal clearance were within the normal range. Blood pH was 7.42 and bicarbonate was 26 mEq/L. Alkaline phosphatase was 464 IU/L (normal 88–271). Liver function tests were within normal limits.

X-ray studies reported as showing slight demineralization of the upper and lower epiphyses of the tibia (Fig 1a) and a cyst-like lesion of the mandible (Fig 2). Neither fracture nor pseudofracture was noted. Immunoreactive parathyroid hormone was 0.10 ng/ml (normal <0.5) and serum calcitonin was 40 pg/ml (normal <30). Serum 25(OH) D_3 measured by competitive protein binding assay (Teijin Bioscience Laboratories) was 15.3 ng/ml (normal 14–42). A diagnosis of osteomalacia secondary to renal phosphate loss was made.

The patient was treated with sodium phosphate ($Na_2HPO_4 \cdot H_2O$) 3 g/day and 1 α

Fig. 1a. X-ray of the tibia (Mar. 27, 1979) shows lucent band in the upper and lower epiphyses.
Fig. 1b. X-ray of the tibia (Jan. 16, 1980) shows marked improvement of lucent change.

Fig. 2. X-ray of the mandible shows radio-lucent cystlike lesion in the middle.

Fig. 3. Serum calcium, phosphorus, and alkaline phosphatase and tubular reabsorption of phosphorus in relation to therapy, Operation (1) ; resection of osteosarcoma of the mandible, MTX ; methotorexate.

Table 1. Values of 25(OH)D₃ and 1, 25(OH)₂D₃ before and after 1α(OH)D₃ treatment.

	25(OH)D ₃ (ng/ml)	1,25(OH) ₂ D ₃ (pg/ml)
Normal	10 - 55	27 - 43
before treatment (April 27, 1979)	15.3	
30 days after treatment (June 20, 1979)	<3.0	177

(OH)D₃ 3 to 24 μg/day. Thirty day after treatment serum phosphorus rose slightly and 1,25(OH)₂D₃ level was higher than normal Table 1). About two months after the treatment, TRP gradually rose to 55-75%, and TmPO₄/GFR rose to 2.0 mg/dl. But serum alkaline phosphatase and clinical symptoms did not change (Fig 3).

On July 27, 1979, the cyst-like tumor of the mandible was resected and was found to be osteosarcoma histologically (Fig. 4). After the operation serum phosphorus level promptly rose to 3.0-3.4 mg/dl, but gradually fell to 2.2-2.7 mg/dl during the next 30 days. On the other hand, TRP rose to 80-85%. The patient improved markedly and he could now walk with some difficulty. For 30 days after the operation, 3400 rad of ⁶⁰Co were given to the mandible and methotorexate (6000 mg) plus folic acid (19 doses of 15 mg) were administered intravenously. On September 13, 1979, reoperation of the mandible was done in order to eradicate the osteosarcoma completely. At that time, bone biopsy from the left iliac crest was done, and revealed typical osteomalacia (Fig. 5, Table 2). Since then, TRP, TmPO₄/GFR and serum

Fig. 4. Photomicrograph of tumor of the mandible showing atypical cell hyperplasia forming osteoid. This is consistent with osteosarcoma. Hematoxylin and eosin stain; magnification $\times 200$.

Fig. 5. Photomicrograph of the iliac crest bone biopsy showing marked increase of osteoid (arrow). Toluidine blue stain: magnification $\times 100$.

Table 2. Histological analysis of the iliac bone.

1) Percent fractional osteoid volume	
	19.6% (normal, <2%)
2) Percent osteoid seams of total surface	
	91.3% (normal, <27%)
3) Partially calcified osteoid (+)	

phosphorus rose to 85-92%, 4.1 mg/dl, and 3.5-4.2 mg/dl, respectively, and remained within normal range without treatment for more than one year (Fig 3). X-ray findings in the tibiae also improved (Fig. 1b). On the other hand, serum alkaline phosphatase was reduced a little but remained higher than normal. At the end of November, 1979, three courses of doxorubicin (one course

was 20 mg $\times$ 3 days) were administered to prevent metastases. The patient returned to work at the end of November, 1979.

DISCUSSION

Danniels and Weisenfeld²³ reported a case of tumorous phosphaturic osteomalacia associated with multiple sclerosing hemangiomas of bone and, in addition, reviewed 16 cases reported previously. Fukumoto et al.¹³ added another case associated with benign osteoblastoma. The tumors were usually vascular with fibrosis and osteoid formation. They were often benign. However, Danniels and Weisenfeld²³ cited two cases associated with sarcoma of the legs reported by Stanbury. Our patient presented with osteosarcoma of the mandible. His symptoms were generalized bone pain and muscle weakness. Hypophosphatemia due to reduced reabsorption of phosphorus by the renal tubule was shown. Serum calcium level was normal and alkaline phosphatase level was markedly elevated. Osteomalacia was proved by the biopsy of the iliac bone. Administration of $1\alpha(\text{OH})\text{D}_3$ and sodium phosphate produced a partial remission, and removal of the sarcoma produced almost complete remission of symptoms and pertinent laboratory data. These are compatible with tumorous phosphaturic osteomalacia reported previously^{13,23}.

There have been some suggestions made concerning the mechanism of osteomalacia in this disorder^{13,43,63}. In the patient presented here, $25(\text{OH})\text{D}_3$ was within normal range before treatment but unfortunately $1,25(\text{OH})_2\text{D}_3$ was not measured. Therefore it was not clear whether or not he had a defect in activating $25(\text{OH})\text{D}_3$. Serum $1,25(\text{OH})_2\text{D}_3$ was elevated above normal after treatment with $1\alpha(\text{OH})\text{D}_3$. On the other hand $25(\text{OH})\text{D}_3$ was suppressed, probably by the large dose of exogenous $1\alpha(\text{OH})\text{D}_3$. At this stage, pertinent laboratory data concerning osteomalacia were improved some but symptoms were not. Therefore, it seemed that inability or difficulty in activating vitamin D_3 was not the sole cause of osteomalacia as

suggested by Drezner and Feinglos⁴⁾. Rather an impaired response of the tubule and bone to active vitamin D₃ might be one of the cause(s). In this regard, mild impairment of proximal tubular function was suggested by the presence of aminoaciduria and microglobulinuria.

Serum alkaline phosphatase level remained high even after removal of osteosarcoma, although clinical symptoms, serum phosphorus level and TmPO₄/GFR had returned to normal and signs of relapse or metastasis of osteosarcoma were not present. The reason for the high alkaline phosphatase is not clear. Follow up observation for the recurrence of osteosarcoma and/or osteomalacia is needed in this case.

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REFERENCES

- 1) Fukumoto Y, Tarui S, Tsukiyama K, et al: Tumor-induced vitamin D-resistant hypophosphatemic osteomalacia associated with proximal renal tubular dysfunction and 1,25-dihydroxy vitamin D deficiency. *J Clin Endocrinol Metab* 49: 873, 1979.
- 2) Daniels RA, Weisenfeld I: Tumorous phosphaturic osteomalacia. Report of a case associated with multiple hemangiomas of bone. *Amer J Med* 67: 155, 1979.
- 3) Dent CE, Stamp TCB: Vitamin D, Rickets, and osteomalacia, chap 5. *Metabolic Bone disease* (Avioli LA, Krane SM, eds), Academic Press Inc, New York, 1977.
- 4) Drezner MK, Feinglos MN: Osteomalacia due to 1 α , 25 dihydroxy cholecalciferol deficiency. *J Clin Invest* 60: 1046, 1977.
- 5) Bijvoet OLM: Renal phosphate excretion in man. *Folia Med Neerl* 15: 84, 1972.
- 6) Harrison HE: Oncogenous rickets: possible elaboration of a humoral substance inhibiting tubular reabsorption of phosphate. *Pediatrics* 52: 432, 1973.