Chronic recurrent multifocal hyperostosis of the long bones associated with hyperphosphatemia—a case report

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A 9-year-old Japanese girl presented in February 1984 with pain in her left lower leg, which had begun without any special event 10 days earlier. There was a tender and slightly warm swelling in the middle third of the left pretibial region. Radiographs of the tibia were normal, but patchy sclerosis of the medullary canal in the diaphysis associated with diffuse periosteal reaction was noticed at a new examination 2 weeks later. The erythrocyte sedimentation rate was 15 mm/hour, C-reactive protein was negative and leukocyte count was normal. A Tc-99m-MDP scan showed abnormal uptake in the left tibia. Osteomyelitis, tumor and bone infarction were considered and open biopsy with curettage was done. Pathology showed periosteal bone formation associated with fibrosis and increased amounts of woven bone associated with fibrosis and vessels in the marrow (Figure 1). Bacteriological examination of biopsy material was negative. Pain was relieved after the biopsy.

She had a similar episode in the right tibia in December 1984. Open biopsy with curettage was done with pathology similar to that in the earlier incident. Pain was again relieved immediately after biopsy.

She had a third attack in the right thigh at the age of 11 years. Radiographs of the femur showed patchy sclerosis of the medullary canal in the diaphysis, associated with periosteal reaction (Figure 2). She was hospitalized for further evaluation.

Physical examination revealed a slender girl (height 143 cm, weight 24 kg) with normal vital signs. Body temperature was normal. Blood cell count and hemoglobin were normal. The erythrocyte sedimentation rate was 11 mm/hour and C-reactive protein was less than 0.3 mg/dL. Bleeding time, coagulation time, urinalysis including urine sediment, pulmonary function tests, blood gas measurements, serum sodium, potassium, chloride, blood urea nitrogen and creatinine were normal.

The serum phosphorus level was high (Table). Calcium and alkaline phosphatase activity were normal. 1-day urinary calcium excretion was normal. The phosphorus excretion index (PEI), calculated as (Up × Scr/Sp × Ucr) − 0.055 × Sp + 0.07 (Sp = serum phosphorus, Up = urine phosphorus, Scr = serum creatinine and Ucr = urine creatinine (Nordin 1964), was markedly reduced. As an index of tubular reabsorptive capacity for phosphorus, Tmp (maximum tubular reabsorption rate of phosphate)/glomerular filtration rate (GFR) was calculated by multiplying Tmp/GFR × 1/Sp, which was read from the nomogram according to Bijvoet and Morgan (1971), by Sp, since tubular reabsorption of phosphorus (TRP), which was cal-

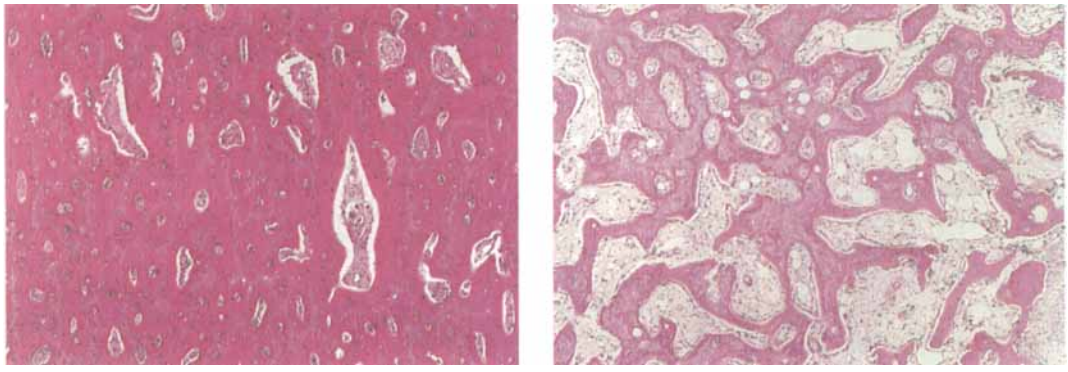
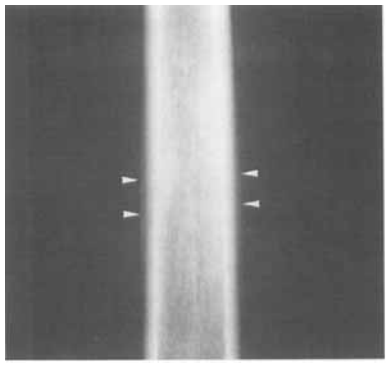


Figure 1. Micrographs of periosteal bone formation from left tibial biopsy specimen (left) and woven bone in marrow from the right tibial specimen (right). The newly formed periosteal bone shows connective tissue in the trabeculae of bone (left). Note woven bone with a lining of osteoblasts and fibrosis-associated vessels in the marrow (right). (HE stain; A x40, B x100).



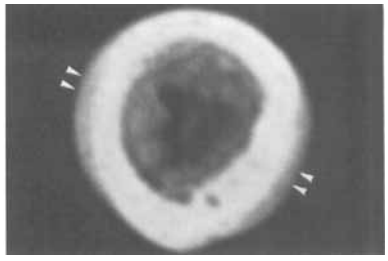


Figure 2. Radiograph and computed tomogram of the femur. Note periosteal reaction (arrowheads) and patchy sclerosis in the medullary canal of the diaphysis.

culated as (1–Up × Scr/Sp × Ucr), was more than 0.80, and the values were remarkably high. The Ellisworth-Howard test was performed using human PTH-(1-34) (Ogata et al. 1984) and phosphaturic and cyclic adenosine 3', 5' monophosphate (c-AMP) responses were normal. Serum C-terminal PTH, intact-PTH, c-AMP and vitamin D metabolite levels were also normal (Table).

Serum vitamin A, vitamin C and thyroid function were normal. All family members (father, mother and 2 brothers) had normal calcium, phosphorus, PEI and Tmp/GFR.

Laboratory findings (normal values in parentheses)

Age (years)	11	11	22
Blood chemistry			
Calcium (mg/dL) (8.6–10.5)	10.0	9.9	9.4
Phosphorus (mg/dL)			
(3.6–5.8 [a], 2.7–4.4 [b])	7.5	7.9	5.7
Alkaline phosphatase (IU/L)			
(66–193 [b])	315	292	115
Creatinine (mg/dL) (0.5–1.0)	0.6	0.6	0.6
C-terminal PTH (ng/mL) (<0.8)	0.5		0.3
Intact-PTH (pg/mL) (<120)	30		43
c-AMP (pmol/mL) (15–37)	16		
Calcitonin (pg/mL) (<170)	22		
25OH vitamin D [c] (ng/mL) (10–55)	24	29	14
1,25(OH)2 vitamin D [d] (pg/mL)			
(20–70 [a], 20–60 [b])	38	50	30.6
24,25(OH)2 vitamin D [c] (ng/mL) (1–4)	1.2	1.9	<0.8
Ellisworth-Howard test			
Phosphaturic response			
(>35 mg/2hours)	41		
Cyclic AMP response			
U4–U3 (>1 µmol/h)	25		
U4/U3 (>10 times)	75		
Urinary excretion			
Calcium (mg/day) (19–212)	182	147	
c-AMP (µmol/day) (1.8–6.3)	4.30	3.42	
Phosphorus excretion index			
(PEI) (–0.09 – +0.09)	–0.28	–0.28	
Tmp/GFR (<5.58)	8.16	8.63	

[a] Values in children
[b] Values in adults
[c] Competitive protein-binding assay
[d] Radio-receptor assay

This girl had similar attacks in the left tibia in January 1987, in the right tibia in May 1987, and in the right radius in July 1987, all of which lasted from several weeks to 3 months. Thereafter, she had similar episodes in both lower legs, but these were so mild that analgesics were not required. Hyperphosphatemia persisted at the age of 22 years (Table).

Discussion

The association of hyperostosis of the long bones and hyperphosphatemia was first described by Melhem et al. in 1970. Since then, 8 patients have been reported (Melhem et al. 1970, Gregoire et al. 1978, Mikati et al. 1981, Talab and Mallouh 1988). Hyperphosphatemia in this condition has been reported to be due to increased renal tubular reabsorption of phosphorus (Mikati et al. 1981), which was confirmed in this study. Since PTH acts to increase phosphorus excretion in the urine, which reduces the serum phosphorus level, this condition may be explained as an insufficiency of PTH (Levi et al. 1992). However, the serum PTH level (Mikati et al. 1981, Talab and Mallouh 1988) and phosphaturic action of exogenous and endogenous PTH were all normal (Mikati et al. 1981); therefore, the renal threshold for phosphorus in this condition must be determined independently of PTH.

1,25(OH)2D is also involved in phosphorus metabolism, and an increase in serum phosphorus causes a reduction of renal vitamin D 1-hydroxylase activity, which reduces the concentration of serum 1,25(OH)2D (Lufkin et al. 1983). However, the vitamin D level has not been evaluated in this condition. In this patient, serum levels of vitamin D metabolites, including 1,25(OH)2D, were normal, suggesting defective regulation of renal vitamin D 1-hydroxylase activity. Thus, not only abnormalities of renal tubular phosphorus transport but also abnormal vitamin D metabolism may play an important pathogenic role; the normal level of 1,25(OH)2D can result in hyper-

phosphatemia by causing both increased gastrointestinal absorption and renal reabsorption of phosphorus (Levi et al. 1992).

Hyperphosphatemia associated with normocalcemia, increased renal tubular reabsorption of phosphorus, normal PTH level and normal phosphaturic response to PTH, and a normal or increased level of 1,25(OH)2D are observed in tumoral calcinosis, which is characterized by deposits of calcium phosphate (Mitnick et al. 1980, Prince et al. 1982, Lufkin et al. 1983). Although patients with both hyperostosis of the long bones and tumoral calcinosis have been reported (Clarke et al. 1984), the relationships between these conditions are unknown.

The symptoms are pain, tenderness and swelling of the long bones, which last several weeks and subside spontaneously, but recur in the same or a different location. The clinical course after 14 years of age is unknown, except in 1 patient: a 24-year-old woman who was still hyperphosphatemic and had the last and mildest attack at 20 years of age (Mikati et al. 1981). Added to my own experience, this condition appears to be less symptomatic with ageing, though hyperphosphatemia persists throughout the individual's life.

This condition should be distinguished from those which have a periosteal reaction and cortical hyperostosis: osteomyelitis, Ewing sarcoma, infantile hyperostosis, pulmonary hypertrophic osteoarthropathy, thyroid acropathy, hypervitaminosis A, scurvy, congenital lues, hemophilia, bone infarction, and Engelman disease (Greenfield 1986). Hyperphosphatemia can be seen in a few conditions, like renal failure, hypo- and pseudohypoparathyroidism, hypervitaminosis D, acromegaly, hypothyroidism, pseudoxanthoma elasticum, as well as tumoral calcinosis (Levi et al. 1992). Our patient had none of the features of these conditions.

The histology of hyperostosis was reported to be normal periosteal bone formation, with vascular connective tissue in 4 cases (Mikati et al. 1981, Talab and Mallouh 1988), whereas the histology of my patient showed increased amounts of woven bone associated with fibrosis in the marrow as well as periosteal bone formation associated with fibrosis. Therefore, from a histological viewpoint, hyperparathyroidism (Ravell 1986), fibrous dysplasia and myelofibrosis should be distinguished from one another.

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