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Oncogenic Osteomalacia : A Clinicopathologic Study of 17 Bone Lesions

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Oncogenic osteomalacia is an unusual and rare clinicopathologic syndrome characterized by mesenchymal tumors that apparently produce osteomalacia and biochemical abnormalities consisting of hypophosphatemia, normocalcemia, and increased levels of alkaline phosphatase. We collected from the Mayo Clinic files and from our consultation files the records for 17 cases of osteomalacia associated with bone lesions. There were five cases of fibrous dysplasia, three of hemangiopericytoma, and two of phosphaturic mesenchymal tumor. There was one case each of osteosarcoma, chondroblastoma, chondromyxoid fibroma, malignant fibrous histiocytoma, giant cell tumor, metaphyseal fibrous defect, and hemangioma. In this study we can figure out that the most common characteristic histologic features of our cases were hemangiopericytomatous vascular proliferation, fine lace-like stromal calcification, and stromal giant cells. In most of the cases, the clinical and biochemical symptoms and signs resolved soon after complete resection of the lesion. When the lesion recurred or metastasized, the symptoms and signs also recurred.

Key Words : *Osteomalacia, hypophosphatemia, hemangiopericytoma, calcification, giant cells.*

INTRODUCTION

Osteomalacia (Greek osteon, bone and malakia, softness) is a defect in the mineralization of the preosseous matrix of mature lamellar bone that leads to an accumulation of nonmineralized or poorly mineralized osteoid over the surfaces of both compact cortical and spongy trabecular bone. During growth, impaired mineralization of the cartilaginous growth plate and primary spongiosa leads to the clinical picture of rickets. After closure of the growth plate, only osteomalacia can occur (Frame and Parfitt, 1978). Histologically, undecalcified bone sections show an increased osteoid volume (Revell, 1986).

The first case of a phosphatemic connective tissue tumor was suggested in 1947 by McCance in a report of "degenerate osteoid tissue" occurring in the distal femur of a 17-year-old girl. In 1956, Hauge reported vitamin D-resistant osteomalacia. In this report, Hauge described a patient with osteomalacia and malignant neurinoma.

Patients with oncogenic or tumorous osteomalacia have mesenchymal tumors that somehow lead to hypophosphatemia, normocalcemia, renal phos-

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phate leak, increased alkaline phosphatase, and osteomalacia. The definition requires that there be no family history of rickets, heavy metal poisoning, or conditions giving rise to Fanconi's syndrome (Thomson et al., 1975 ; Drezner and Feinglos, 1977 ; Daniels and Weisenfeld, 1979 ; Ryan and Reiss, 1984 ; Weidner et al., 1985, 1987 ; Sparagana, 1987). The most distinctive radiologic features of adult osteomalacia are the presence of Looser's zones or pseudofractures, indistinctiveness or loss of bone trabecular structure, and nonspecific decrease in bone radiodensity. These radiologic findings can be confirmed by bone biopsy. This oncogenic or tumor-induced osteomalacia is an unusual and interesting syndrome usually manifested in early adult life. The clinical course is typically protracted. In some cases, the initial clinical presentation is mistaken for rheumatoid arthritis, muscular dystrophy, or primary neurologic disorder. In some instances, a pathologic fracture is the first sign (Ryan et al., 1986).

The oncogenic cause of osteomalacia may be unrecognized because the tumors are frequently small (e.g., a 1-cm tumor of the big toe [Weidner and Santa Cruz, 1987]), asymptomatic, or appear several years after the recognition of osteomalacia (Nuovo et al., 1989).

Our study was undertaken to examine the histologic features of bone lesions, especially focussing on whether there are any histologic hallmarks to suggest the presence of osteomalacia.

MATERIALS AND METHODS

From the Mayo Clinic files of more than 9,500 bone tumors and tumorous conditions, we found 8 examples of lesions associated with osteomalacia and 12 additional cases from the consultation files of more than 20,000 cases. Three of these had to be discarded because the biopsy showed no pathologic features in one case and family history of osteomalacia in another case. The third case was a soft tissue tumor with histologic features of phosphaturic mesenchymal tumor, as described recently (Weidner and Santa Cruz, 1987). We reviewed microscopic slides including Hematoxylin-Eosin staining of specimens from all cases. We also reviewed some of the reticulin stain slides. In two of our cases, we were unable to clearly define specific features that would permit a unified diagnosis. Because these two cases showed mixed connective tissue variants. We adopted Weidner and Santa Cruz's method (Weidner and Santa Cruz, 1987) to classify these oncogenic osteomalacia tumors as phosphaturic mesenchymal tumor.

Clinical information and follow-up data were obtained from the patients' medical records and the consultation letters. Preoperative radiographs were reviewed in 14 cases. Follow-up information was obtained by correspondence with the outside physicians.

RESULTS

patients with the age consisted of 9 males and 8 females, ranging from 3 to 76 years. According to the original pathologic diagnosis, there were 5 cases of fibrous dysplasia, 3 of hemangiopericytoma, and 2 of atypical fibrous histiocytoma. The rest of the cases include on each of malignant fibrous histiocytoma, fibroblastic osteosarcoma, chondroblastoma, chondromyxoid fibroma, giant cell tumor, metaphyseal fibrous defect, and hemangioma(Table 1). The patient in the last case had evidence of involvement of the clavicle, thoracic and lumbar spine, left proximal femur, and a rib with hemangioma on bone scans.

Among the five cases of fibrous dysplasia, four were polyostotic. Four patients with fibrous dysplasia had Albright's syndrome, as reported previously (McArthur et al., 1979). The case of atypical fibrous histiocytoma of the femur, that of hemangiopericytoma of the ischium, and that of metaphyseal fibrous defect of the femur have been reported (Linovitz et al., 1976 ; Firth et al., 1985 ; Nuovo et al., 1989), as has the case of osteosarcoma arising from the navicular bone (Cheng et al., 1989). We have reclassified atypical fibrous histiocytoma of the femur

Table 1. Diseases Causing Oncogenic Osteomalacia in 17 Patients

Diagnosis	No. of patients
Fibrous dysplasia	5
Hemangiopericytoma	3
Phosphaturic mesenchymal tumor	2
Osteosarcoma, fibroblastic	1
Chondroblastoma	1
Chondromyxoid fibroma	1
Malignant fibrous histiocytoma	1
Giant cell tumor	1
Metaphyseal fibrous defect	1
Hemangioma, multiple	1

and osteosarcoma of the navicular bone as phosphaturic mesenchymal tumor. The case of hemangiopericytoma of the femur has also been reported (Schultze et al., 1989). Six lesions involved the femur, four the tibia, two the rib, and one each the ilium, ischium, fibula, navicula, and humerus (Table 2).

Table 2 Summary of Findings in 17 Patients With Oncogenic Osteomalacia

Patient	Age, yr	Sex	Diagnosis	Location of lesion	Calcium,[1] mmol/L	Phosphorus,[2] mmol/L	Alkaline phosphatase,[3] U/L	Parathyroid hormone[4]	Radiograph[5]	Follow-up, length[6]	Status	Reference
1	41	F	Giant cell tumor	Ilium	2.33	0.42↓	Not done	Normal	Negative	None	Not known	···
2	13	F	Metaphyseal fibrous defect	Femur	2.5	0.55↓	173↑	Normal	Positive	1 mo	Doing well	Drezner and Feinglos, 1977
3	46	M	Hemangiopericytoma	Ischium	2.35	0.32↓	69↑ (normal, 9-39)	Not done	Negative	None	Not known	Linovitz et al., 1976
4	14	F	Chondroblastoma	Tibia	Normal	0.58↓	680↑↑	480 pg/mL (normal, 100-360 pg/mL)	Positive	7 yr	Doing well	···
5	31	M	Malignant fibrous histiocytoma	Fibula	Not done	HypoP	Not done	Not done	Negative	3 yr	Doing well	···
6	55	F	Phosphaturic mesenchymal tumor	Navicula	2.43	0.60↓	527↑↑	1.2 ng/mL (normal, <0.4 ng/mL)	Not done	22 mo	Doing well	Cheng et al., 1989
7	27	M	Fibrous dysplasia	Rib	2.23↓	0.91↓	Not done	Not done	Not done	None	Not known	···
8	58	M	Hemangiopericytoma	Femur	2.0↓	0.52↓	740↑↑	432 pg/mL (normal, 80-340 pg/mL)	Not done	2 yr	Doing well	Schultze et al., 1989
9	76	F	Hemangiopericytoma	Humerus	HypoCa	HypoP	Not done	Not done	Negative	6 mo	Doing well	···
10	13	M	Chondromyxoid fibroma	Tibia	2.4	1.13↓	185↑	Not done	Positive	61 yr	Doing well	···
11	3	F	Fibrous dysplasia (polyostotic)	Femur	2.25↓	0.58↓	272↑	14.28 pmol/l	Positive	32 yr	Died	McArthur et al., 1979
12	6	M	Fibrous dysplasia (polyostotic)	Femur	2.7	0.71↓	1,018↑↑↑	1.56 pmol/L	Negative	28 yr	HP	McArthur et al., 1979
13	48	M	Phosphaturic mesenchymal tumor	Femur	2.43	0.39↓	109↑	0.41 pmol/L	Negative	28 yr	Doing well	Firth et al., 1985
14	7	F	Fibrous dysplasia (polyostotic)	Femur	2.38	0.79↓	1,008↑↑↑	4.44 pmol/L	Positive	12 yr	HP	McArthur et al., 1979
15	8	F	Fibrous dysplasia (polyostotic)	Tibia	2.48	1.0↓	624↑↑	9.12 pmol/L	Negative	14 yr	HP	McArthur et al., 1979
16	33	M	Multiple hemangioma	Rib	2.4	0.58↓	433↑	Not done	Negative	None	Not known	···
17	7	M	Osteosarcoma	Tibia	2.43	0.81↓	995↑↑	Not done	Positive	1 yr	Doing well	···

HP : high level of alkaline phosphatase, HypoCa : hypocalcemia, HypoP : hypophosphatemia, ↑ : mild increase, ↑↑ : moderate increase, ↑↑↑ : severe increase, ↓ : mild decrease.

1) Mayo reference range, 2.3 to 2.8 mmol/L.

2) Mayo reference range, 0.78 to 1.52 mmol/L for adults and 1.29 to 2.26 mmol/L for children.

3) Mayo reference range, 20 to 90 U/L.

4) Mayo reference range, <6.1 pmol/L.

5) Positive or negative findings for osteomalacia.

6) Month-to-month or year-to-year.

Radiographs were available for study in 14 of the cases. Radiologically, there were diffuse nonspecific decreases in radiodensity, coarsening of bony trabeculae, and pseudofracture in six patients. The growth plates were widened in six patients : one each with metaphyseal fibrous defect (patient 2 in Table 2), chondroblastoma, chondromyxoid fibroma (Fig. 1), fibrous dysplasia (patient 11), fibrous dysplasia (patient 14, Fig. 2), and osteosarcoma (Fig. 3 A and B). Only one patient with open growth plates had physes that appeared normal.

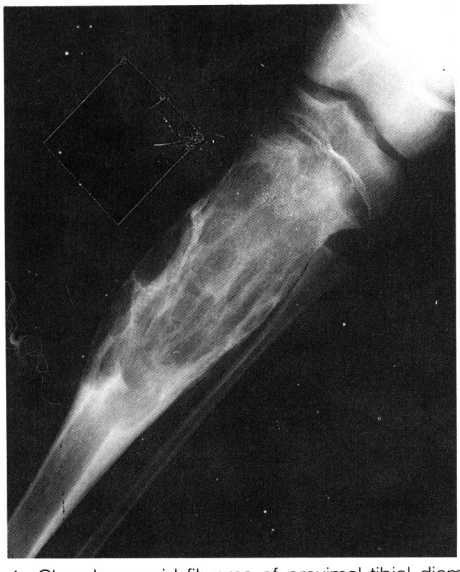

Fig. 1. Chondromyxoid fibroma of proximal tibial diametaphysis, with widened growth plates on both sides of knee joint.

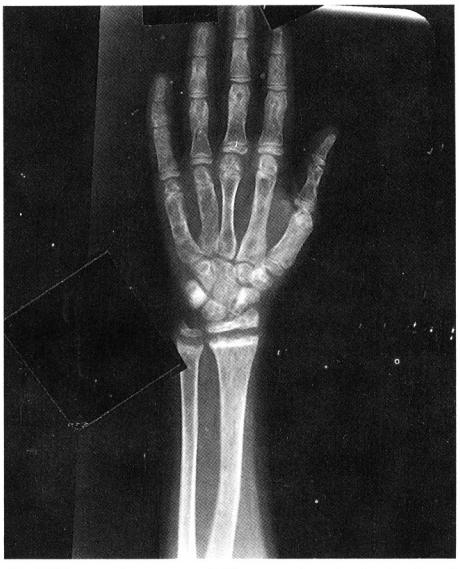

Fig. 2. Diffuse changes of fibrous dysplasia in the hand and forearm. The growth plates of the distal radius and ulna are widened.

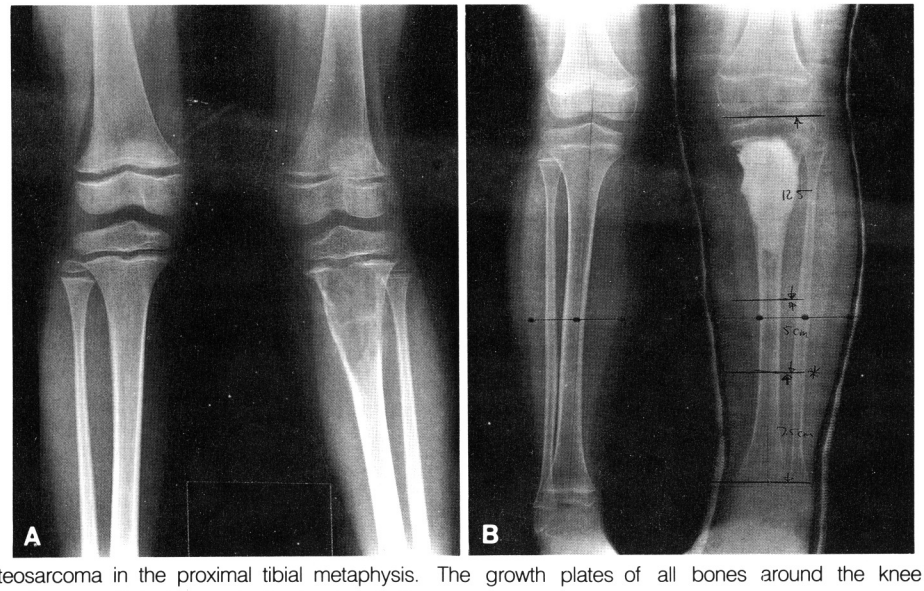

Fig. 3. Osteosarcoma in the proximal tibial metaphysis. The growth plates of all bones around the knee were wide before chemotherapy, A, but normal after treatment, B.

Clinical Symptoms and Signs

Among the consultation cases, information about clinical symptoms was available for eight patients. The patients showed easy fatigability, pain in an affected joint, intermittent discomfort, and a fracture of the affected bone with minor trauma. These symptoms developed 1 to 8 years before the disease was diagnosed. Among the Mayo Clinic patients, four with polyostotic fibrous dysplasia had frequent fractures, abnormal waddling gait, and bowing and deformity of the leg by age 2 to 5 years. Others had leg pain, back pain, muscle weakness, cramps, and stiffness of 1 to 8 years in duration.

The laboratory data were available for the nine consultation cases. Five patients had normocalcemia, and three had a slight decrease in calcium level (information about serum level of calcium was not available for one patient). All nine patients were hypophosphatemic, alkaline phosphatase values were available for five patients, and they were increased in all of them. Parathyroid hormone levels were analyzed in five patients and were increased in three. The level of 1,25-dihydroxyvitamin D3 was measured in three patients : in one the level was decreased and in the two others it was normal. There were normocalcemia, hypophosphatemia, and increased alkaline phosphatase levels in all eight Mayo Clinic patients. Of the five Mayo Clinic patients whose parathyroid hormone levels were known, the level was increased in two and normal in three.

Follow-Up Information

Follow-up information was obtained from seven Mayo Clinic patients and six consultation patients. Among the clinic patients, the one with chondromyxoid fibroma had no evidence of osteomalacia either clinically or biochemically during the 61 years of follow-up. Among the four clinic patients with polyostotic fibrous dysplasia, one (patient 11 in Table 2) had persistent hypophosphatemia and increased alkaline phosphatase levels. This patient died after 32 years of follow-up. The three other patients with polyostotic fibrous dysplasia had follow-up ranging from 12 to 28 years. They showed persistent increase in alkaline phosphatase levels. However, the serum calcium and phosphorus levels were within normal limits. One patient with phosphaturic mesenchymal tumor (patient 13) was followed up for 28 years. During this period, there was one recurrence of the tumor in the femur and three surgical resections of metastatic foci in the lung. Each time the tumor recurred or metastasized, the serum phosphorus level decreased and the alkaline phosphatase level increased ; however, after the resection of recurrence or metastasis, the values returned to normal limits. This patient is now well clinically, with normal levels of phophorus and alkaline phosphatase. The patient with multiple hemangioma has been lost to follow-up. The patient with osteosarcoma had preoperative chemotherapy and resection. Radiologic evidence indicated that the rickets resolved with chemotherapy.

In the consultation series, six patients were followed up from 1 month to 7 years. None of these patients showed evidence of hypophosphatemic osteomalacia, either clinically or biochemically. Metabolic abnormalities resolved soon after surgical treatment in patients with metaphyseal fibrous defect (patient 2), phosphaturic mesenchymal tumor (patient 6), and hemangiopericytoma (patients 8 and 9). Patients 1 (giant cell tumor), 3 (hemangiopericytoma), and 7 (fibrous dysplasia) were lost to follow-up. Among the patients with hemangiopericytoma, two were followed for 6 months (patient 9) and 2 years (patient 8). During follow-up, they were well and without evidence of osteomalacia. Two patients (6 and 13) with phosphaturic mesenchymal tumor were followed up for 22 months and 28 years. Both were well and without evidence of disease during the follow-up period. The biochemical hypophosphatemia resolved 3 weeks postoperatively in one patient (17) with osteosarcoma. Radiographically, four patients with widened growth plates showed healed osteomalacia 4 months postoperatively.

Pathologic Findings

Three patients with hemangiopericytoma showed proliferation of round-to-oval cells around deformed vascular spaces, with a staghorn appearance (Fig. 4). One lesion showed lattice-like fine trabecular calcification, and one tumor had spotty punctate calcification.

In phosphaturic mesenchymal tumor, the lesions consisted mainly of spindle cells that had an interlacing pattern, with moderate amounts of collagen (Fig. 5). Both lesions showed a slit-like vascular pattern throughout, and one had a focal heman-

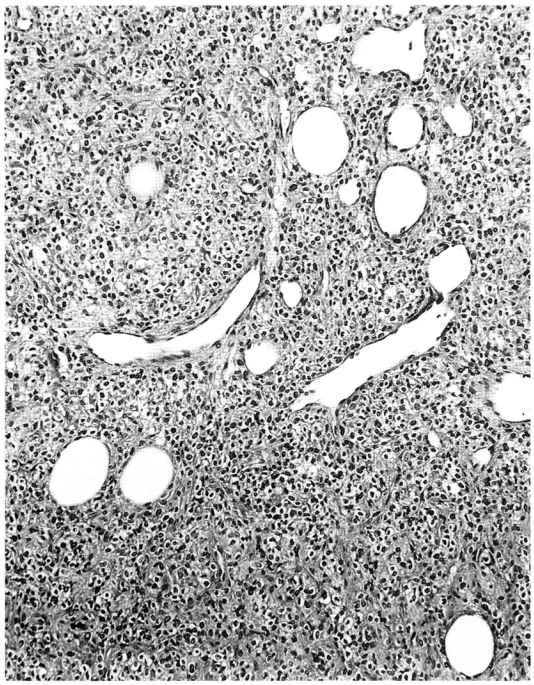

Fig. 4. Hemangiopericytoma with proliferation of pericytes and slit-like vascular spaces(×160).

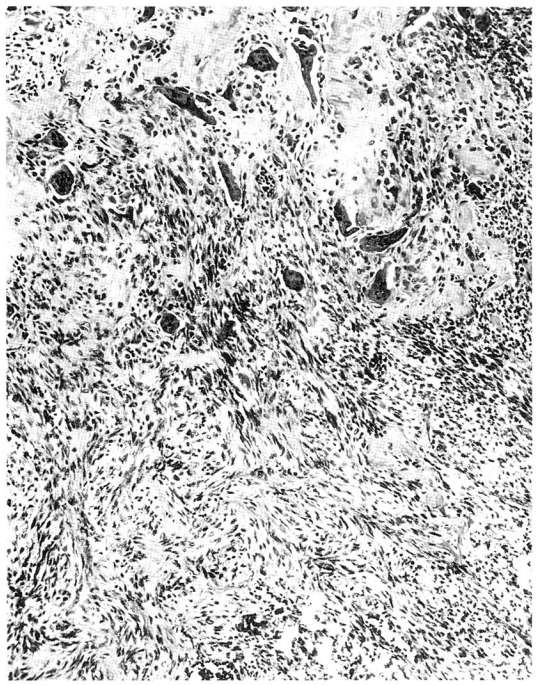

Fig. 5. Phosphaturic mesenchymal tumor with storiform pattern and collagen formation(×100).

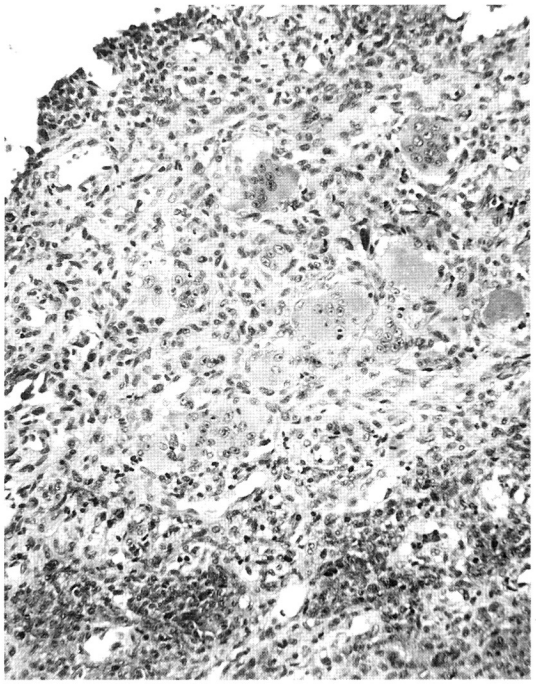

Fig. 6. Phosphaturic mesenchymal tumor with patchy distribution of giant cells(×250).

giopericytomatous pattern. Two lesions contained a moderate number of giant cells that had a patchy distribution (Fig. 6). Two tumors showed mild--to-moderate amounts of lattice-like calcification (Fig. 7). Individual tumor cell nuclei were plump and vesicular-to-spindle-shaped. There were occasional mitoses and focal plasma cell infiltrations.

The one example of malignant fibrous histiocytoma showed a storiform pattern of spindled malignant tumor cells (Fig. 8). There was diffuse proliferation of capillary-sized blood vessels with a focal hemangiopericytomatous pattern (Fig. 9). There were large numbers of giant cells. Calcification was heavy in this case. The calcification patterns varied from fine granular punctate to fairly large masses (Fig. 10). The tumor cells showed moderate pleomorphism and mitotic activity.

Among the five patients with fibrous dysplasia, four had polyostotic fibrous dysplasia. All the remaining of lesions had features typical of fibrous dysplasia, grade 4 fibroblastic osteosarcoma, chondroblastoma, chondromyxoid fibroma, giant cell tumor, metaphyseal fibrous defect, and hemangioma.

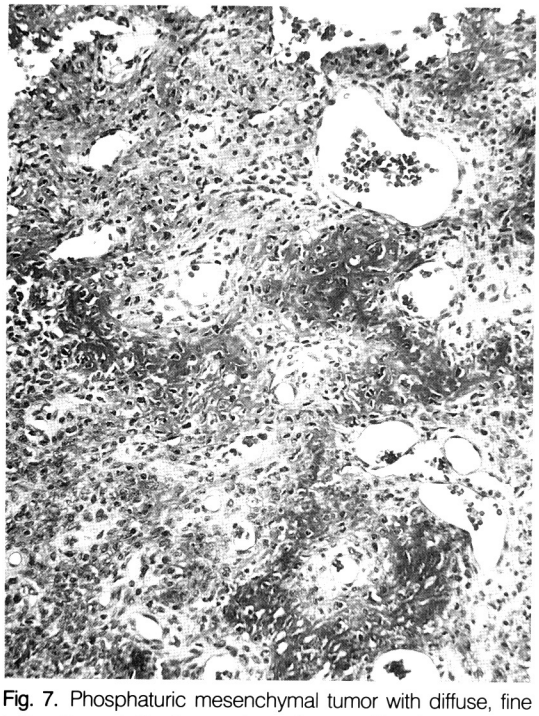

Fig. 7. Phosphaturic mesenchymal tumor with diffuse, fine lattice-like calcification and capillary proliferation between tumor cells(×250).

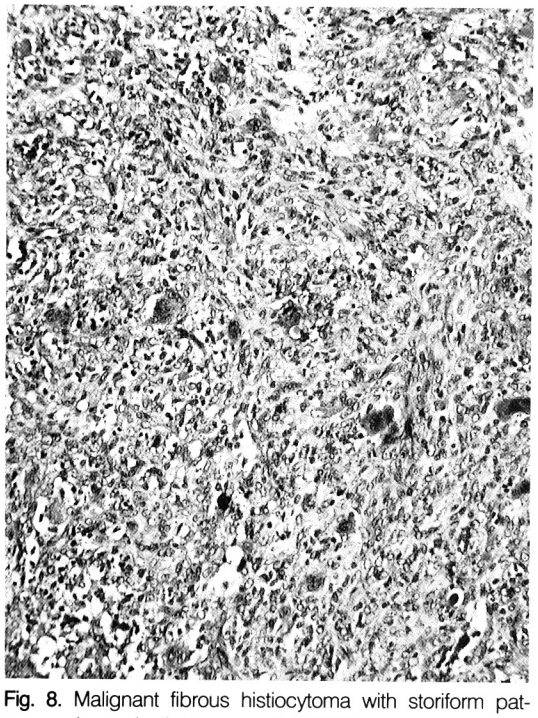

Fig. 8. Malignant fibrous histiocytoma with storiform pattern and anaplastic tumor cells(×250).

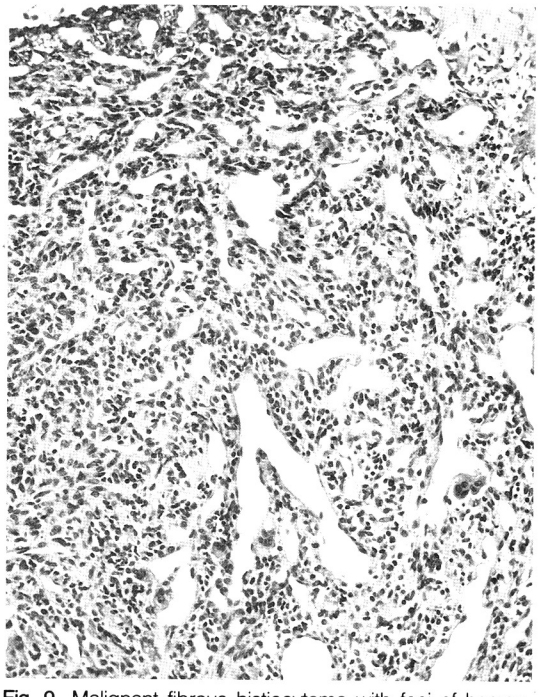

Fig. 9. Malignant fibrous histiocytoma with foci of hemangiopericytomatous vascular proliferation(×250).

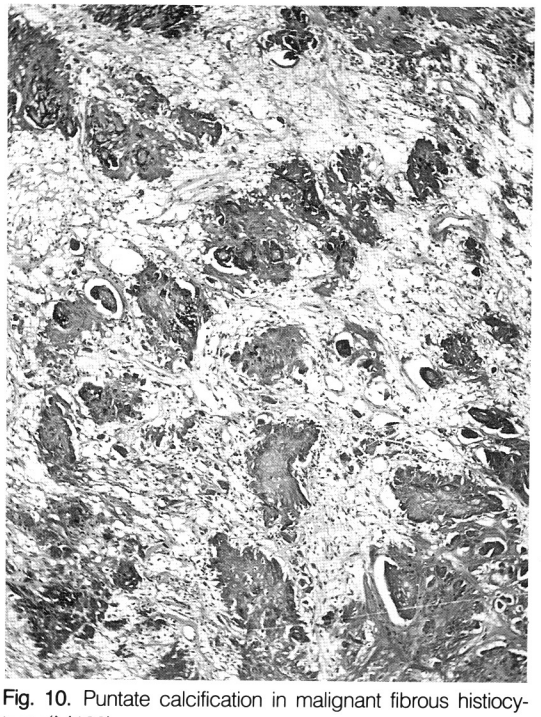

Fig. 10. Puntate calcification in malignant fibrous histiocytoma(×100).

DISCUSSION

Oncogenic osteomalacia is an interesting disease entity first described by Prader et al. in 1959 in an 11-year-old girl with a giant cell reparative granuloma of the rib. Including the cases in our series, more than 100 cases have been described.

In our study, the most characteristic histologic findings were the presence of capillary-sized, slit-like hemangiopericytomatous vascular proliferation, matrix calcification, and giant cells. A hemangiopericytomatous slit-like, capillary vascular proliferative pattern was identified in 50% of our cases. A hemangiopericytomatous vascular pattern is seen in various bone sarcomas, including osteosarcoma and mesenchymal chondrosaroma. However, it is not common in any tumor except mesenchymal chondrosaroma. In our experience, hemangiopericytoma as a primary bone neoplasm is very uncommon ; there are only 14 examples in the Mayo Clinic files of 9,500 primary bone neoplasma. So the three examples in this small series are remarkable. Among the 17 tumors, 7 showed dystrophic matrix calcification, and in 5 there was diffuse-to-focal fine lattice-like calcification. The rest of the lesions showed punctate or grouped calcification. The lace-like matrix calcification is very characteristic and often suggests the possibility of hypophosphatemic osteomalacia. However, calcification is not always seen and not all the tumors with calcification occur in patients with the syndrome. Calcification is common in bone neoplasms such as chondroblastoma and osteosarcoma. However, the peculiar patchy matrix dystrophic calcification seen in seven tumors in our series is quite distinctive. This calcification is unlike that seen in the matrix of osteosarcoma. The distinctive calcification and the presence of hemangiopericytomatous slit-like capillary vascular proliferation in some of the other neoplasms suggest an association with osteomalacia.

Of the lesions, 60% contained multinucleated giant cells. Giant cells were irregularly distributed in all but one lesion, and the number of giant cells was highly variable. Weidner et al. (1985) concluded from their electron microscopic study that the giant cells were osteoclast-like in appearance. Various studies have suggested that the osteoclast-like multinucleated giant cells are not critical in the pathogenesis of oncogenic osteomalacia (Aschinberg et al., 1977 ; Yoshikawa et al., 1977 ; Lyles et al., 1980, 1982).

It is apparent that phosphaturic mesenchymal tumors represent a heterogeneous group. The terminology for these primitive tumors is still a matter of controversy. Olefsky et al. (1972) suggested the term "ossifying mesenchymal tumor associated with osteomalacia". However, not all tumors contain ossified areas, and it is sometimes difficult to differentiate reactive bone formation from true tumoral bone. Salassa et al. (1970) suggested the term "sclerosing hemangioma". Other authors have used such descriptive terms as "benign angiofibroma" (Cotton and Van Puffelen, 1976), "hemangiopericytoma" (Linovitz et al., 1976), "chondrosarcoma" (Firth et al., 1985), "primitive mesenchymal tumor" (Weidner et al., 1985). The diversity of these diagnostic terms underscored the morphologic complexity of the tumors and the difficulty in developing a single universally acceptable term (Weidner and Santa Cruz, 1987). In 1987, Weidner and Santa Cruz suggested that until the specific cell type or phosphaturic substance is characterized, it is best to use a descriptive phrase to label these tumors. The diagnostic phrase they preferred for the tumors occurring in soft tissue was "phosphaturic mesenchymal tumor (mixed connective tissue variant)." For those occurring in bone resembling osteoblastomas, they favored the phrase "phosphaturic mesenchymal tumor (osteoblastoma-like variant)."

The most frequent symptoms our patients experienced were easy fatigability, painful joints, intermittent muscle cramps, muscle weakness, stiffness, and fractures of affected bones. Patients with oncogenic osteomalacia have symptoms for several years before the tumor is recognized(in our series, the duration of symptoms was as long as 8 years), perhaps because this paraneoplastic syndrome is rare and clinicians are not aware of it (Weidner et al., 1985). The patients usually have hypophosphatemia, normal or slightly low serum levels of calcium, and increased levels of alkaline phosphatase. Of the three patients whose levels of 1,25-dihydroxyvitamin D3 were known, one had a decreased level, as described by Sweet et al. (1980). There are several reports of normal levels of 1,25-dihydroxyvitamin D3 in patients with oncogenic osteomalacia(Lever and Pettingale, 1983 ; Cotton and Van Puffelen, 1986 ; Clinicopathologic conference, 1987 ; Papotti et al., 1988 ; Case records, 1989 ; Nuovo et al., 1989). The patients tend to be classified as rheumatic, neurologic, or even

psychiatric (Moser and Fessel, 1974). Soon after the tumor is removed, the clinical symptoms and the abnormal biochemical features usually resolve (Weidner et al., 1985, 1987 ; Nuovo et al., 1989).

Among the four patients with polyostotic fibrous dysplasia, three had persistently increased levels of alkaline phosphatase. The patient with multiple hemangioma also had persistent hypophosphatemia and increased levels of alkaline phosphatase. This probably reflected the extensive nature of their disease, which could not be surgicallyl treated. One patient with phosphaturic mesenchymal tumor had one recurrence of the lesion and three metastases in association with the reappearance of the biochemical abnormalities, with or without accompanying symptoms.

Usually, a dramatic reversal to a normal bone metabolism occurs after the benign tumor is excised. Seven of our consultation patients and one Mayo Clinic patient did not show evidence of hypophosphatemia and increased alkaline phosphatase after removal of the lesions. It is well documented that incomplete removal of the primary lesions or recurrence is indicated by reappearance of hypophosphatemia and bone pain (Nuovo et al., 1989).

Medical therapy for osteomalacia, consisting of increasing dosages of vitamin D or phosphatate (generally both were needed), provided only a transitory improvement in approximately 15% of patients (Nuovo et al., 1989). Other therapeutic modalities include amputation (Nuovo et al., 1989), surgical correction of deformity (Evans et al., 1980), radiotherapy (Gitelis et al., 1986 ; Miyauchi et al., 1988), and chemotherapy for primary lesions (Nomura et al., 1981). Recurrence of the primary lesion, which was suspected because of reappearance of the biochemical features with or without accompanying symptoms, was seen in our case of aypical fibrous histiocytoma, in cases of hemangiopericytoma of bone (McClure and Smith, 1987) and soft tissue (Miyauchi et al., 1988), and in a case of maxillary sinus mesenchymal tumor (Weidner et al., 1985).

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