Phosphaturic Mesenchymal Tumors

A Polymorphous Group Causing Osteomalacia or Rickets

NOEL WEIDNER, MD,* AND DANIEL SANTA CRUZ, MD†

Reported are the pathologic features of 17 mesenchymal tumors documented as causing osteomalacia or rickets. Although these tumors were histologically polymorphous, they were classifiable into four morphological groups. In the first group there were ten unique tumors showing mixed connective tissue features and containing variably prominent vascular and/or osteoclast-like giant-cell components. Tumors of this group also displayed focal microcystic changes, osseous metaplasia, and/or poorly developed cartilaginous areas. The cartilaginous areas sometimes showed considerable dystrophic calcification. With one exception, all tumors of this group occurred in soft tissue and demonstrated benign clinical behavior. The single malignant tumor originated in bone, recurred locally, and metastasized to lung. The tumors comprising the remaining three groups (six tumors) occurred in bone, demonstrated benign clinical behavior, and were grouped according to their close resemblance to tumors known to occur in bone, that is osteoblastoma-like (four tumors), nonossifying fibroma-like (two tumors), and ossifying fibroma-like (one tumor).
***Cancer* 59:1442–1454, 1987.**

ONCOGENIC or tumor-induced osteomalacia or rickets is characterized by renal phosphate wasting and hypophosphatemia. In this disease available data indicates that a tumor produces a renal phosphaturic substance or hormone that depletes total-body phosphates by reducing tubular reabsorption of phosphate.[1,2] Although concomitant deficiency of 1,25-dihydroxyvitamin-D3 may be contributory in some cases, after sufficient phosphate has been lost, osteomalacia or rickets develops. When the tumor is discovered and removed, the renal phosphate wasting stops and the osteomalacia or rickets resolves.

It is important to emphasize that these tumors are frequently very small and occur in peculiar locations making discovery difficult (*e.g.*, a 1-cm tumor of the big toe).[1-3] As a consequence, the syndrome often persists unrecognized for many years before the tumor is discovered and removed. In addition to hypophosphatemia, inappropriate phosphaturia, and decreased levels of 1,25-dihydroxyvitamin-D3 levels these patients have elevated serum levels of alkaline phosphatase.[1,2] Serum levels of calcium and immunoreactive parathyroid hormone have been normal in most cases.[1,2] Therefore, whenever a patient develops this biochemical profile (with or without nonnutritional osteomalacia or rickets), the physician should consider tumor-induced disease and search for a small, inconspicuous tumor.

Weidner *et al.*[1] recently have reported the pathologic features of three mesenchymal tumors causing osteomalacia or rickets and reviewed case reports wherein tumors were completely documented as causing this fascinating syndrome. As a result of this study, it became clear that pathologists have given these tumors a variety of descriptive morphologic labels. Some of these tumors are difficult to classify and may be labelled with different diagnostic descriptors, depending upon the reviewing pathologist.[1] This confusion has persisted, because the literature incompletely describes and illustrates many of the tumors, and no single institution has analyzed a large number of cases. However, from the initial review by Weidner *et al.*,[1] it was apparent that approximately 87% of these tumors contained multinucleated giant cells and approximately 80% had prominent vascularity. These findings, plus the histologic features of the three reported cases,

From the *Department of Pathology, Wake Forest University, Bowman Gray School of Medicine, Winston-Salem, North Carolina, and †St. John's Mercy Medical Center, St. Louis, Missouri.

Address for reprints: Noel Weidner, MD, Department of Pathology, Harvard Medical School, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115.

The author thanks the following physicians for providing representative case material (listed alphabetically): Russell S. Asnes (New York), S. Boriani (Bologna, Italy), M. Campanacci (Bologna, Italy), G.E. Cotton (Duluth, Minnesota), John D. Crawford (Boston), Elliott Foucar (Albuquerque, New Mexico), Yasuaki Fukumoto (Osaka, Japan), T. Imamura (Tokyo, Japan), Hirosh Kida (Ishikawa, Japan), Bruce D. Mason (Ottumwa, Iowa), I. Reid (St. Louis, Missouri), Robert M. Salassa (Rochester, Minnesota), Edward H. Soule (Rochester, Minnesota), H.C. Taylor (St. Louis, Missouri), Alexander C. Templeton (Chicago), and M.P. Whyte (St. Louis, Missouri).

Accepted for publication November 14, 1986.

suggested that the so-called "heterogeneous" group of mesenchymal tumors causing osteomalacia or rickets could, in fact, represent a morphologic spectrum of a unique tumor.

To overcome these uncertainties and help clarify this problem, we solicited representative tumor material from authors known to have published well-documented cases of oncogenic osteomalacia or rickets. The solicited material was then combined with five cases already in our possession. The analysis of that material (17 cases) constitutes the basis of this report (Table 1).

Methods and Materials

Representative tumor material was solicited by mail from authors known to have published well-documented examples of oncogenic osteomalacia or rickets. In these cases the bone and metabolic disturbances improved or completely disappeared upon removal of the tumor. In addition to the five cases already in the possession of the current authors, 12 additional cases were collected.[4-7,9-14] The solicited materials were hematoxylin & eosin stained slides (ten cases), paraffin-embedded tissue (one case), plastic-embedded tissue for ultrastructural studies (two cases), and six representative photographs (5 × 7 inches each) of the only available histologic slide. This material was combined with material already possessed by the current authors, which included paraffin-embedded tissue (five cases) and plastic-embedded tissue (four cases). The clinical and laboratory features of these cases are described in the accompanying table and in their corresponding literature reports.

Four tumors were studied immunohistochemically using standard immunoperoxidase techniques.[15] Three of these tumors (7, 9, and 10) (all paraffin-embedded tissue) were studied for immunoreactivity to cytokeratin (clones AE-1/AE-3, Hybritech, San Diego, CA), chromogranin (clone LK2H10, Hybritech), leu-M1 (clone CD15, Becton-Dickinson, Mountain View, CA) vimentin (Biogenex Labs; Dublin, CA 94568), desmin (clone DE-R-11; Dakopatts, Santa Barbara, CA), leukocyte common antigen (clones PD7-26/2B11, Dakopatts), Factor VIII-related antigen (Dakopatts), S-100 (Dakopatts), and neuron-specific enolase (Dakopatts). Before cytokeratin and desmin antigens were assayed, slides were pretreated with 0.2% trypsin for 10 and 20 minutes, respectively. The fourth tumor (Case 3) had already been studied for immunoreactivity to keratin, S-100 protein, Factor VIII-related antigen, and *Ulex europaeus 1*-lectin binding as previously described.[1] Standard electron-microscopic techniques[16] were employed for ultrastructural studies of six tumors (3, 4, 7, 8, 9, and 10). The ultrastructural findings for tumors 3 and 4 have been previously reported.[1]

Results

The 17 phosphaturic mesenchymal tumors were subclassifiable into four morphologic groups. The first and largest group (ten cases) was composed of a peculiar form of mixed connective tissue tumor that occurred predominantly in soft tissues and contained variably prominent vascularity and osteoclast-like giant cells. Tumors of the remaining three groups occurred in bone and were grouped according to their close resemblance to tumors known to occur in bone, that is osteoblastoma-like tumors (four cases), nonossifying fibroma-like tumors (two cases), and an ossifying fibroma-like tumor (one case).

Phosphaturic mesenchymal tumors from patients 1 through 10 were classified descriptively as mixed connective tissue variants. The patients' ages ranged from 27 to 63 years (average, 44 years); five were women. All tumors were located in soft tissues except the single malignant example (Case 8), which appeared to arise from a femoral condyle. These tumors were composed of small, round to spindled, mesenchymal cells that showed fibroblast-like differentiation and grew in sheets containing (in various combinations) clusters of osteoclast-like giant cells (Figs. 1A and 1B), microcystic areas (Figs. 2A and 2B), prominent blood vessels (Figs. 3A & 3B), poorly formed cartilaginous areas (Figs. 4A and 4B), and foci of osseous metaplasia.[1] The cartilaginous areas were colloidal-iron positive both before and after hyaluronidase digestion, and these areas sometimes contained dystrophic calcification (Figs. 5A & 5B), which were positive by the von Kossa stain for calcium. The blood vessels formed patterns similar to those found in hemangiopericytomas (Figs. 3A and 3B).

Immunohistochemical studies of the tumors from Cases 7, 9, and 10 revealed only vimentin immunoreactivity within the primitive-appearing tumor cells. All other reagents (desmin, S-100 protein, leu-M1, chromogranin, cytokeratin, neuron-specific enolase, leukocyte common antigen, and Factor VIII-related antigen) were nonreactive in tumor cells. In addition and as previously reported, immunohistochemical studies of tumor 3 revealed no immunoreactivity for S-100 protein, cytokeratin, Factor VIII-related antigen, and no *Ulex europaeus 1*-lectin binding in tumor cells.[1]

Ultrastructural studies of tumors 4, 7, 9, and 10 revealed oval to spindled, stromal cells having irregular nuclei and inconspicuous nucleoli (Figs. 6 and 7A). Their cytoplasm contained occasional lysosomes, lipid vacuoles (Figs. 7A and 8), variable numbers of mitochondria, scattered profiles of rough endoplasmic reticulum, small vesicles (Fig. 6, inset), and sometimes abundant intermediate filaments (Fig. 7A). No neurosecretory granules were found. These cells were separated by an intercellular matrix composed

TABLE 1. Clinicopathologic Features of Phosphaturic Mesenchymal Tumors Causing Osteomalacia/Rickets

Case	Reference	Age at onset/sex	Age at excision, location & initial tumor diagnosis	Final descriptive classification	Bone findings		Time until*		Comments
					Osteopenia	Biopsy results	Chem resp	Clin resp	
1	Salassa *et al.*[4]	34/M	38 yr; Lt groin mass; 3–4 cm; "sclerosing hemangioma with focal bone"	Mixed connective tissue variant	+	ND	10 d	2 d	AWED 16 yr later
2	Salassa *et al.*[4]	27/F	30 yr; Rt thigh mass; 2 × 3 cm; "sclerosing hemangioma"	Mixed connective tissue variant	+	Osteomalacia	3 wk	6 mo	AWED 16 yr later
3	Weidner *et al.*[1]	35/F	39 yr; Rt maxillary sinus, "primitive mesenchymal tumor"	Mixed connective tissue variant	+	Osteomalacia	1 d	4 d	AWED 3 yr later
4	Weidner *et al.*[1]	33/M	34 yr; Lt Palm lesion, soft tissue, 4.5 cm, "soft parts chrodroma-like with giant cells"	Mixed connective tissue variant	+	Osteomalacia	1 d	1 d	AWED 8 yr later
5	Weidner *et al.*[1]	63/F	66 yr; Lt distal ulna, bone & soft tissue, "osteocartilaginous mesenchymal tumor"	Mixed connective tissue variant	+	ND	3 mo	3 wk	AWED 2 yr later
6	Cotton and Van Puffelen[5]	45/F	48 yr; soft tissue mass, Rt knee, "benign angiofibroma"	Mixed connective tissue variant	+	Osteomalacia	5 d	4 mo	AWED 9 yr later
7	Gitelis *et al.*[6]	44/F	50 yr; soft tissue mass, Lt forearm, 7 cm, "hemangiopericytoma"	Mixed connective tissue variant	−	Osteomalacia	5 d	1 yr	AWED 19 mo later
8	Firth *et al.*[7]	44/M	49 yr; cystic lesion of Rt femoral condyle; tumor recurred locally at 52 yr; AKA performed; Pulm lesions resected at 53 yr & 55 yr; "chondroblastoma/ chondrosarcoma"	Mixed connective tissue variant	−	Osteomalacia	Within days	NC	Alive with disease 6 yr later
9	Taylor *et al.*[8]	61/M	61 yr; soft tissue mass of Rt deltoid region; 1.5 cm; patient also had multiple dermatofibromas; "benign mesenchymal neoplasm"	Mixed connective tissue variant	+	Osteomalacia	2 wk	Within weeks	AWED 2.5 yr later
10	Taylor *et al.*[8]	57/M	57 yr; soft tissue mass of Rt ankle; 4.0 cm; "mixed connective tissue tumor"	Mixed connective tissue variant	+	Osteomalacia	Within days	Within weeks	AWED 0.5 yr later

11	Yoshikawa *et al.*[9]	13/M	18 yr; 4th metacarpal, "osteoblastoma"	Osteoblastoma-like variant	+	Osteomalacia	1 wk	11 wk	AWED 14 wk later
12	Yoshikawa *et al.*[9]	13/F	18 yr; lytic lesion, upper humerus, "osteoblastoma"	Osteoblastoma-like variant	+	Osteomalacia	2 d	1 d	AWED 10 wk later
13	Fukumoto *et al.*[10]	24/F	24 yr; lytic lesion, tibia, 4.5 cm, "osteoid with osteoblasts"	Osteoblastoma-like variant	"Looser's zones"	Osteomalacia	1 wk	Within weeks	AWED 5 mo later
14	Boriani and Companacci[11]	18/M	19 yr; osteolytic sacral lesion, "osteoblastoma"	Osteoblastoma-like variant	+	ND	1 yr	1 yr	AWED 32 yr later
15	Pollack *et al.*[12]	7.5/M	12 yr; lytic lesion, distal radius, 2.8 cm, "nonossifying fibroma"	Nonossifying fibroma-like variant	"Rickets"	ND	4 d	1 yr	AWED 1 yr later
16	Asnes *et al.*[13]	13/F	14 yr; cortical defect, Lt femur, 1.5, cm, "nonossifying fibroma"	Nonossifying fibroma-like variant	+	ND	1 d	3 mo	AWED 3 mo later
17	Nomura *et al.*[14]	27/M	29 yr; cystic mandibular lesion, "osteosarcoma"	Ossifying fibroma-like variant	+	Osteomalacia	Within days	Within months	1 recurrence 1.5 mo later, treated at 2nd surgery, AWED 5 yr later

* Time until chemical response (Chem Resp.) and/or clinical response (Clin Resp) after tumor removal. These times are often imprecisely stated in the corresponding literature reports.

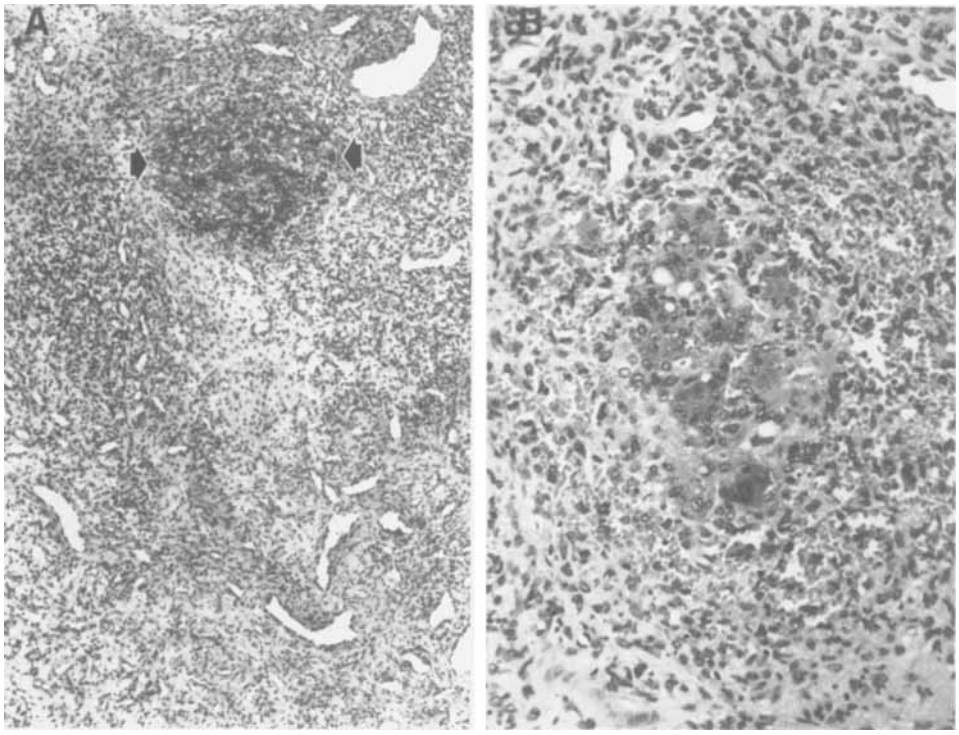
AWED: alive without evidence of disease; ND: not done; NC: not clear; Lt: left; Rt: right; Pulm: pulmonary.

of collagen fibers and matrix granules sometimes forming globular aggregates and containing dystrophic calcification (Fig. 7A). Within tumor 9 one endothelial cell contained parallel crystalline arrays which were partially surrounded by cell membrane and associated with electron-dense material (Fig. 7B). The significance of these latter structures remains unclear, but they could represent crystallized secretion products.

Ultrastructural studies of tumor 8 revealed osteoclast-like giant cells admixed with variably differentiated round to oval-shaped, mononuclear cells. The latter appeared to form an ultrastructural continuum ranging from poorly differentiated small polygonal cells to cells with fibrohistiocytic features (Fig. 8). Like the primitive-appearing mesenchymal cells of tumor 3,[1] the small, poorly differentiated, polygonal cells of tumor 8 had round or slightly irregular nuclei, inconspicuous nucleoli, and evenly distributed chromatin (Fig. 9). Their nuclei were surrounded by organelle-poor cytoplasm containing occasional mitochondria, lysosomal granules, lipid vacuoles, intermediate filaments, or strands of rough endoplasmic reticulum. These poorly differentiated cells were sometimes found in close contact with adjacent osteoclast-like giant cells (Fig. 9). The fibrohistiocytic cells of tumor 8 had larger more irregular nuclei with coarser chromatin and more prominent nucleoli. Their cytoplasm had more abundant mitochondria, lysosomal granules, lipid vacuoles, intermediate filaments, and strands of rough endoplasmic reticulum. Indeed, the complexity of the cytoplasm of the fibrohistiocytic cells approached that of the osteoclast-like giant cells. Mononuclear cells of all types formed rare, primitive, cell-to-cell junctions and showed focal villiform cytoplasmic borders. In all the cells examined no neurosecretory granules were found.

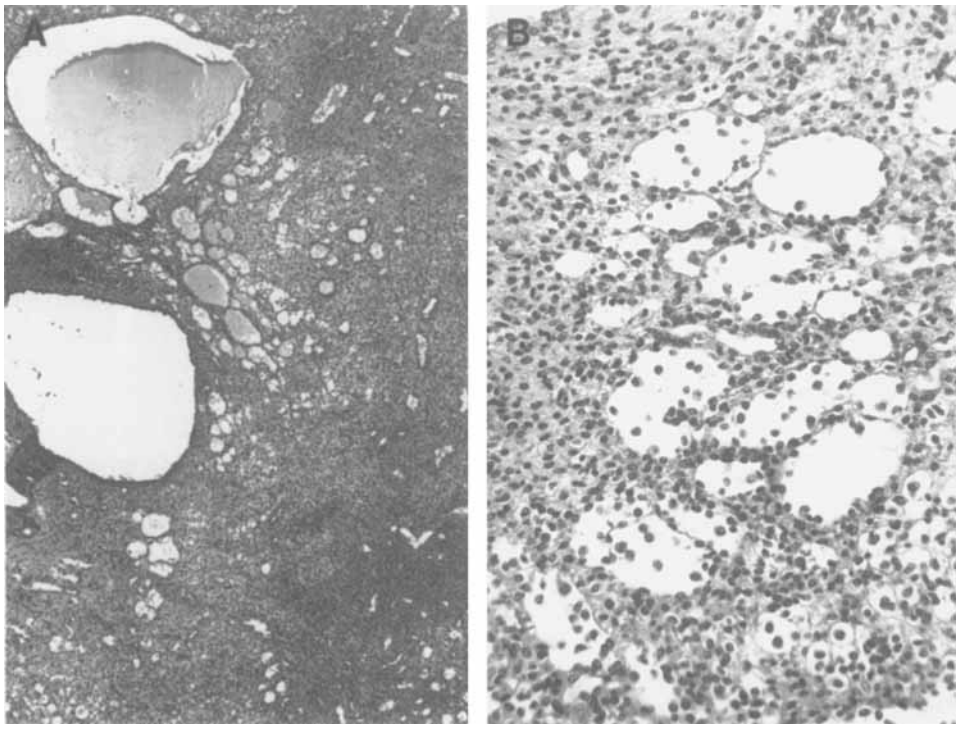
Follow-up in these 10 cases has ranged from 0.5 to 16 years (average, 5.5 years). All except one (Case 8) have followed a benign course. The malignant example recurred locally and metastasized to the lungs. The patient remains alive but with persistent metabolic abnormalities, presumably the consequence of residual tumor. Although morphologically similar to other tumors in this first group, it displayed denser nuclear chromatin, increased anisonucleosis, and greater mitotic activity (1-3 mitotic figures per 10 high-powered fields). The other mixed connective tissue tumors (1–7, 9, and 10) displayed homogeneous nuclear features, even chromatin distribution, and rare mitotic figures.

Tumors from Patients 11 through 14 were classified as osteoblastoma-like tumors. The patients' ages ranged from 13 to 24 years (average, 17 years); two were women. All these tumors occurred in bone. These tumors were benign cytologically and were composed of vascular, osteoblastic fibrous tissue in which abundant (sometimes confluent) osteoid had been irregularly deposited (Figs. 10A and 10B,

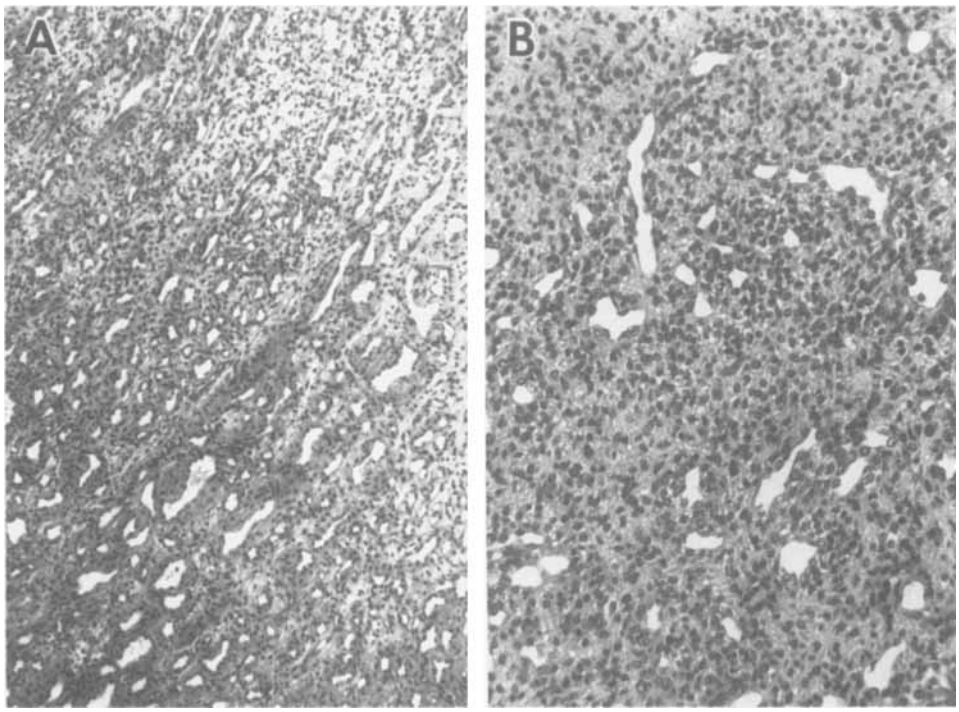


FIGS. 1A AND 1B. Case 2 (phosphaturic mesenchymal tumor, mixed connective tissue variant). (A) Cellular stroma composed of primitive-appearing stromal cells containing prominent vascularity and a cluster of osteoclast-like giant cells (arrows) (H & E, original magnification ×10). (B) Cluster of osteoclast-like giant cells surrounded by hemorrhagic, poorly differentiated stroma composed of small, round to spindle-shaped mesenchymal cells (H & E, original magnification ×62.5).

11A and 11B). Osteoclast-like giant cells were scattered between the osteoid which was frequently rimmed by osteoblasts and contained nests of histiocytic foam cells (Fig. 11B). Follow-up in these four cases has been from 2.5 months to 32 years; all have thus far followed a benign course.

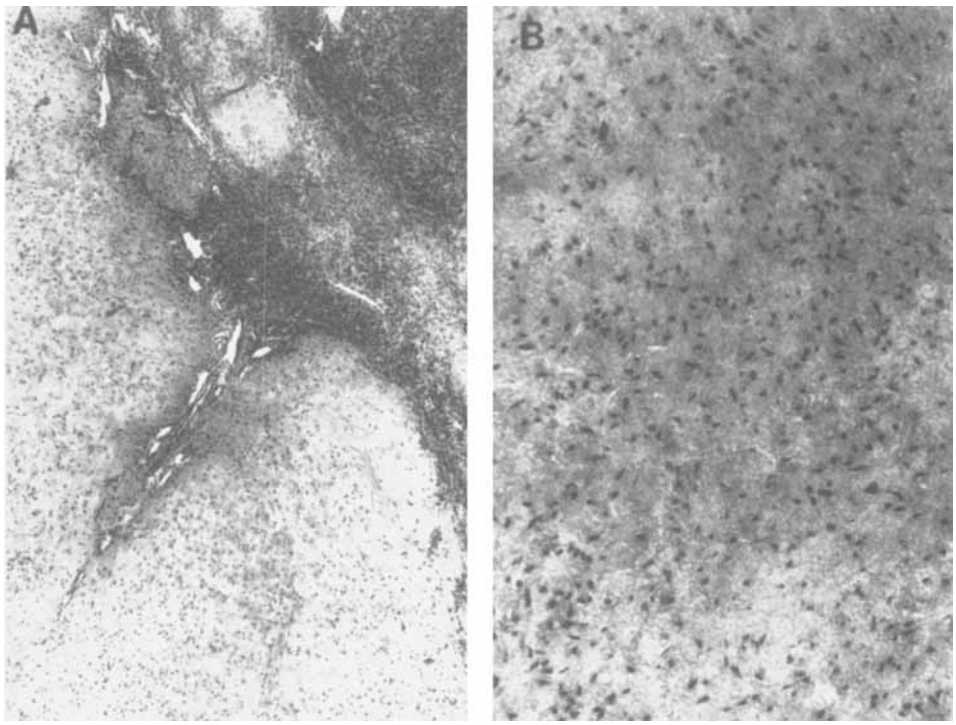


FIGS. 2A AND 2B. Case 7 (phosphaturic mesenchymal tumor, mixed connective tissue variant). (A) Low-power field showing variably sized microcystic changes within tumor stroma. Some of the microcystic spaces are filled with proteinaceous material (H & E, original magnification ×5). (B) Microcystic spaces shown in greater detail (H & E, original magnification ×62.5).

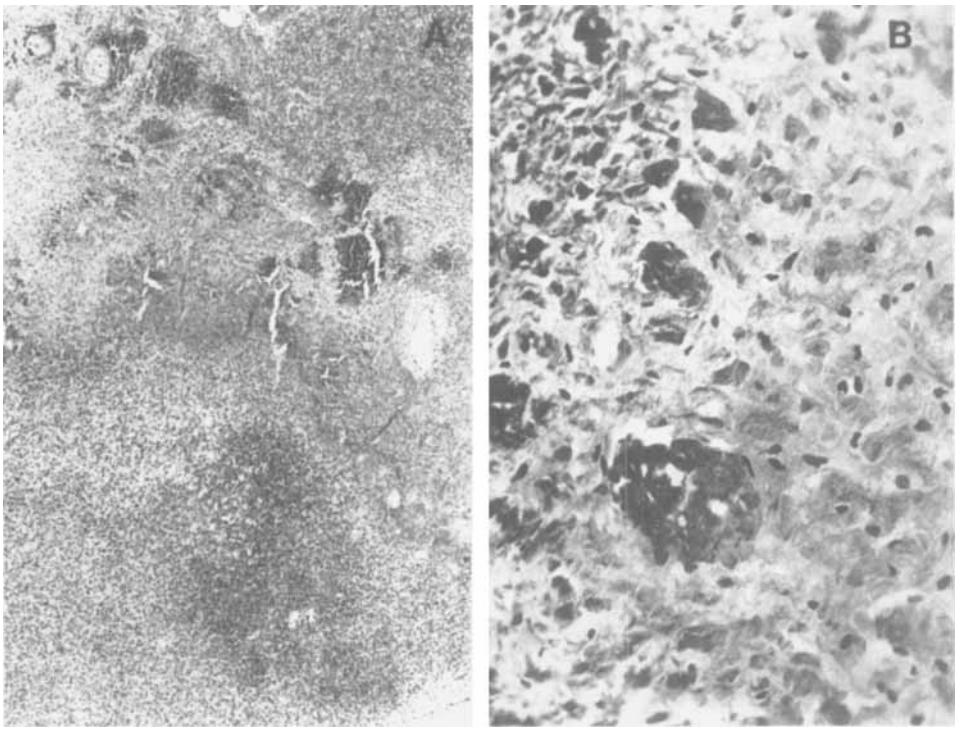


FIGS. 3A AND 3B. Case 7 (phosphaturic mesenchymal tumor, mixed connective tissue variant). (A) Low-power view of the tumor stroma containing numerous vessels in hemangiopericytoma-like pattern (H & E, original magnification ×10). (B) High-powered view of primitive-appearing stroma showing capillary-like vascular spaces forming hemangiopericytoma-like pattern (H & E, original magnification ×62.5).

Tumors from patients 15 and 16 were like nonossifying fibromas. The patients' ages were 7.5 and 13 years; one was a woman. Both tumors occurred in bone and were benign cytologically. They were composed of spindle cells disposed in a whorled storiform pattern containing scattered osteoclast-like giant cells and focal hemorrhages (Fig.



FIGS. 4A AND 4B. Case 9 (phosphaturic mesenchymal tumor, mixed connective tissue variant). (A) Lobulated cartilage-like stroma surrounds primitive-appearing stroma containing osteoclast-like giant cells (arrows) (H & E, original magnification ×5). (B) High-power view of primitive-appearing stroma having a cartilage-like appearance. These areas were colloidal-iron positive both before and after hyaluronidase treatment, and yet they were S-100 protein negative (H & E, original magnification ×62.5).



FIGS. 5A AND 5B. Case 10 (phosphaturic mesenchymal tumor, mixed connective tissue variant). (A) Primitive-appearing stroma showing diffuse areas of dystrophic calcification and a tendency to develop cracking artifact during paraffin sectioning of blocks (H & E, original magnification ×5). (B) High-power field showing cartilage-like stroma containing foci of dystrophic calcification (H & E, original magnification ×100).

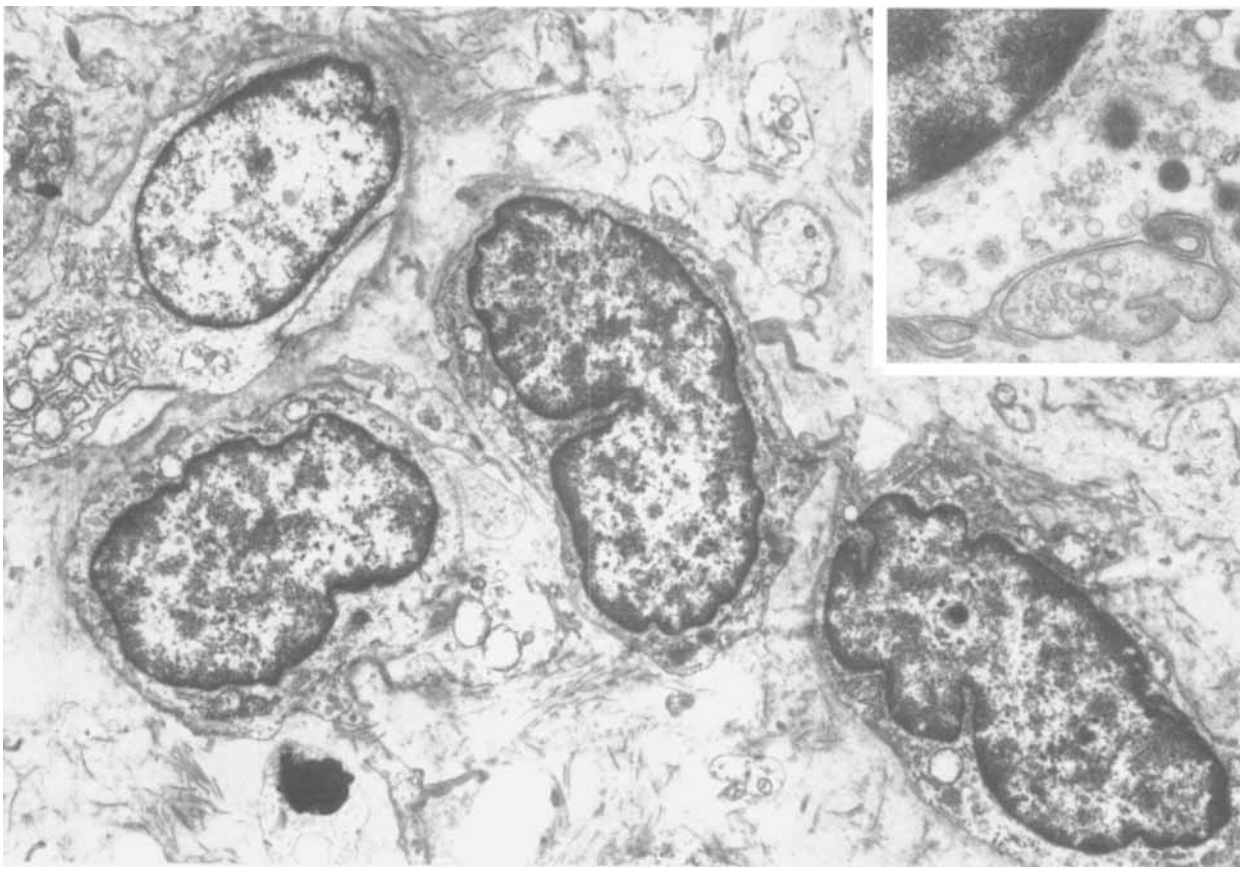
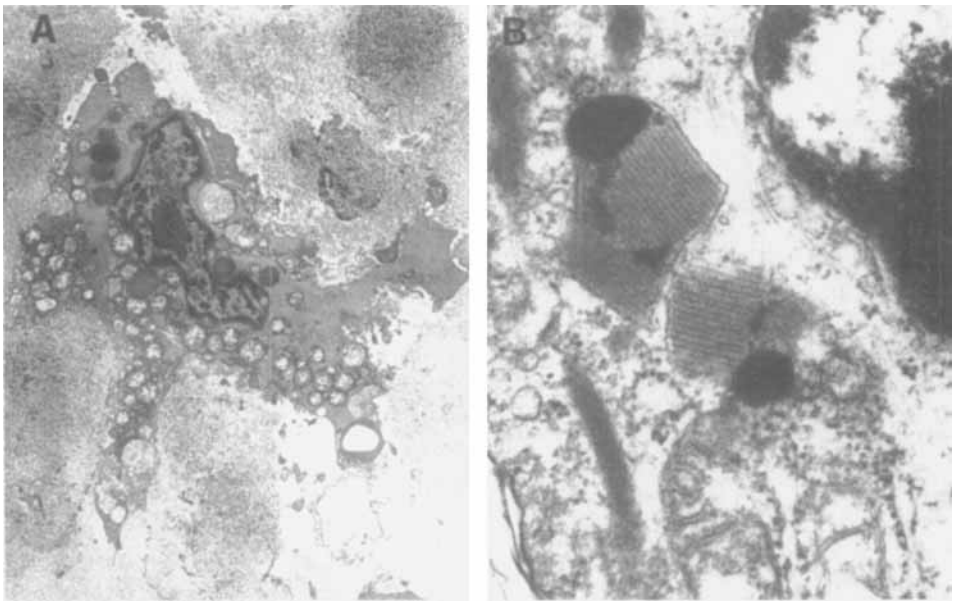


FIG. 6. Case 7 (phosphaturic mesenchymal tumor, mixed connective tissue variant). Ultrastructural features of the primitive-appearing stromal cells are shown. Notice the oval to spindled shape of the cells, the slightly irregular nuclei, and the scant cytoplasm containing a few profiles of rough endoplasmic reticulum, occasional mitochondria, and rare lysosomes. The intercellular matrix contains collagen fibers and very finely granular matrix (lead citrate and uranyl acetate, ×6000). *Inset:* Cytoplasmic vesicles which were frequently present in these cells are shown. No neurosecretory granules were found (lead citrate and uranyl acetate, ×12,000).



FIGS. 7A AND 7B. Case 10 (phosphaturic mesenchymal tumor, mixed connective tissue variant) (A) Stromal cell containing irregular nucleus and cytoplasm. The cytoplasm demonstrates abundant intermediate filaments (vimentin by immunohistochemical studies), numerous mitochondria, and scattered lipid vacuoles. The intercellular matrix contains numerous matrix granules (focally aggregated) showing early dystrophic calcification (lead citrate and uranyl acetate, ×3000). (B) Endothelial-cell cytoplasm containing peculiar parallel crystalline arrays, partially surrounded by plasma membrane and associated with electron-dense material. Wiebel-Palade bodies are also present (lead citrate and uranyl acetate, original magnification ×12,000).

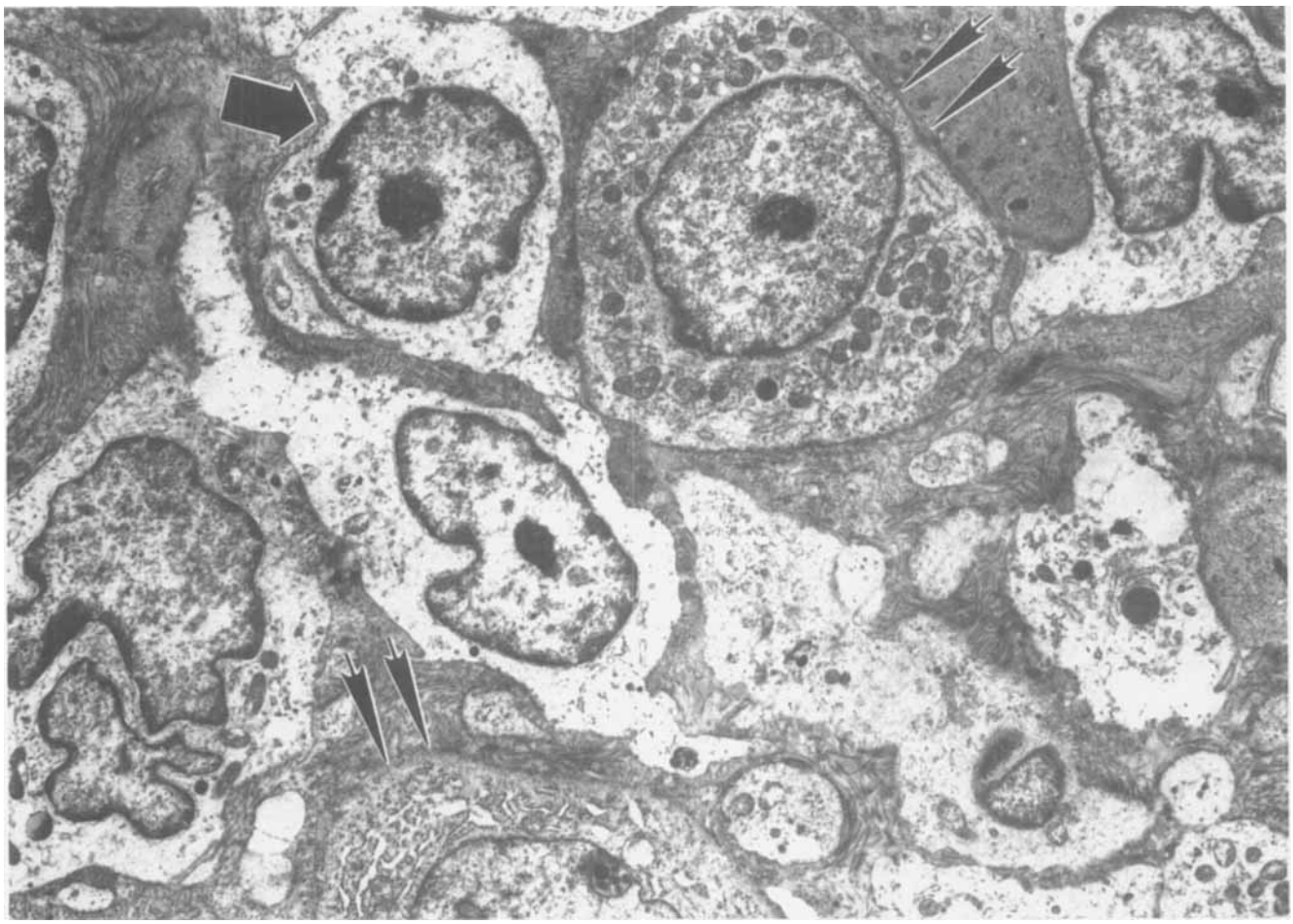


FIG. 8. Case 8 (malignant phosphaturic mesenchymal tumor, mixed connective tissue variant). Round to spindled mesenchymal cells showing features ranging from poorly differentiated, small cells containing organelle-poor cytoplasm (single broad arrow) to fibrohistiocytic cells containing organelle-rich cytoplasm (double arrows). The complexity of the latter approached that found in osteoclast-like giant cells (uranyl acetate and lead citrate, original magnification ×2500).

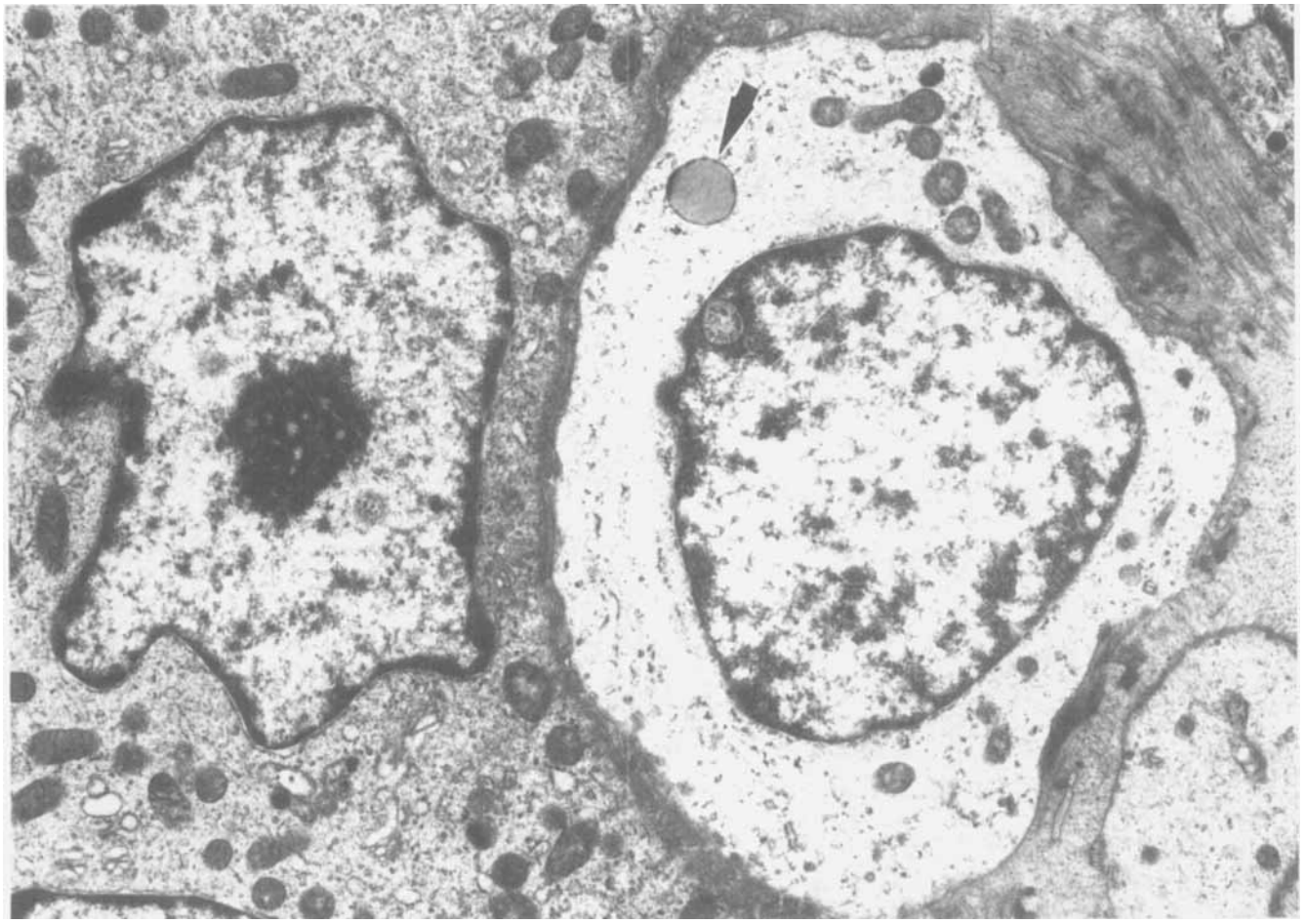


FIG. 9. Case 8 (malignant phosphaturic mesenchymal tumor, mixed connective tissue variant). Primitive-appearing, small mesenchymal cell is organelle-poor containing a few mitochondria, occasional strands of rough endoplasmic reticulum, rare intermediate filaments, and a single lipid vacuole (arrow). Portions of its cytoplasmic border touches, and is partially surrounded by, the cytoplasm of an osteoclast-like giant cell (uranyl acetate and lead citrate, original magnification ×5500).

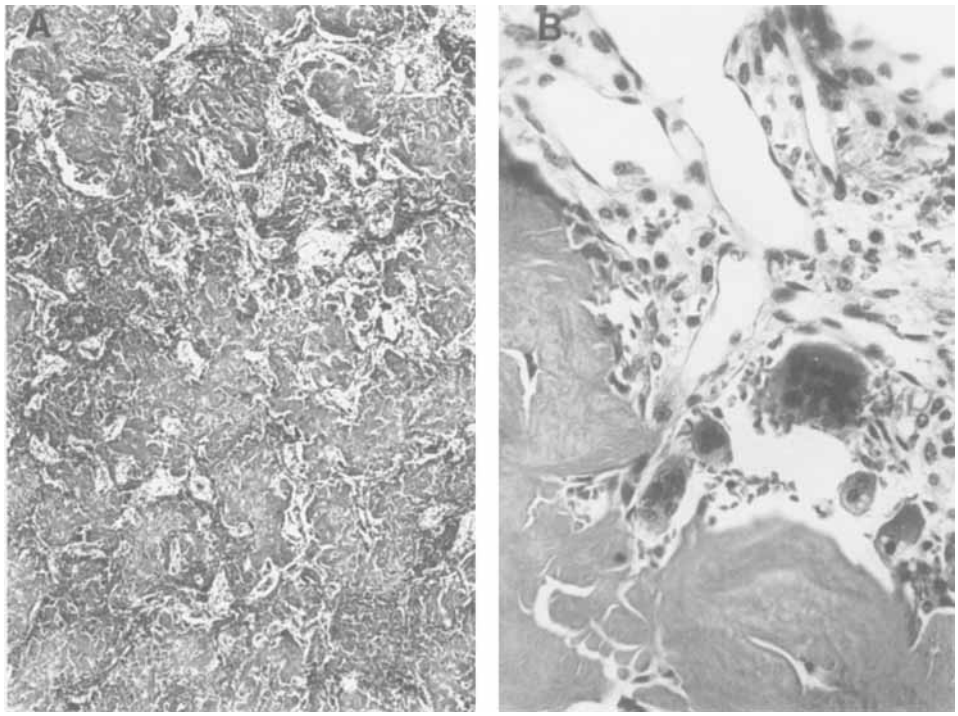
12A). Vascularity was minimally developed. Follow-up varied from 3 to 13 months, and thus far both tumors have followed a benign course.

The tumor from patient 17 most closely resembled ossifying fibroma. This patient was a man, age 27 years. His tumor was composed of swirling bundles of spindle cells that were arranged in fascicles and storiform patterns. Between the spindle cells were scattered osteoclast-like giant cells and areas of osteoid (Fig. 12B). Vascularity was moderately developed. Cytologically the nuclei were slightly atypical and there were 1 to 2 mitotic figures per 10 high-powered fields. Although this tumor recurred 1.5 months after the initial surgery, following the second resection the patient remained alive and well without evidence of tumor 5 years later.

Discussion

Even though a number of well-documented cases of oncogenic osteomalacia or rickets have been reported, confusion persists regarding the morphologic features of tumors that cause this fascinating syndrome. Olefsky and co-workers,[17] as well as Evans and Azzopardi,[18] have stressed the probable similarity of these tumors. However, Yoshikawa *et al.*[9] as well as Weidner and co-workers[1] were unable from their case studies and literature reviews to clearly define specific features that would permit a unified diagnosis. This has largely resulted from the rarity of this syndrome, which has precluded morphologic analysis of a large number of these tumors at one institution. To overcome these problems, representative material from 17 tumors known to have caused osteomalacia or rickets were collected and reviewed.

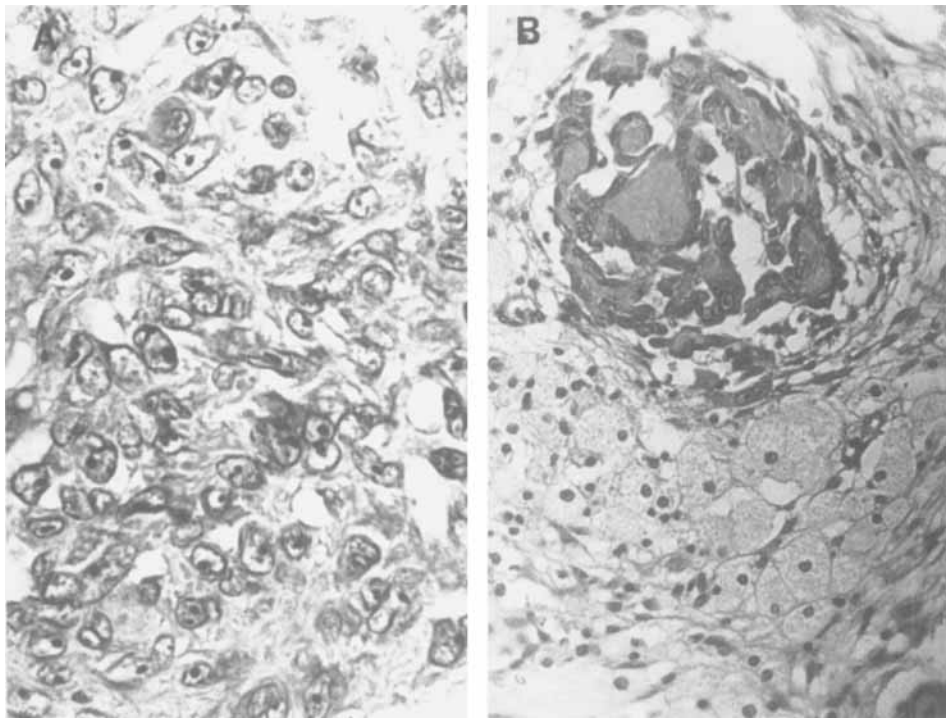
It became clear from our analysis of 17 tumors that, although these phosphaturic mesenchymal tumors were histologically polymorphous, they were roughly classifiable into four morphologic patterns. These included primitive-appearing, mixed connective tissue tumors (ten cases), osteoblastoma-like tumors (four cases), nonossi-



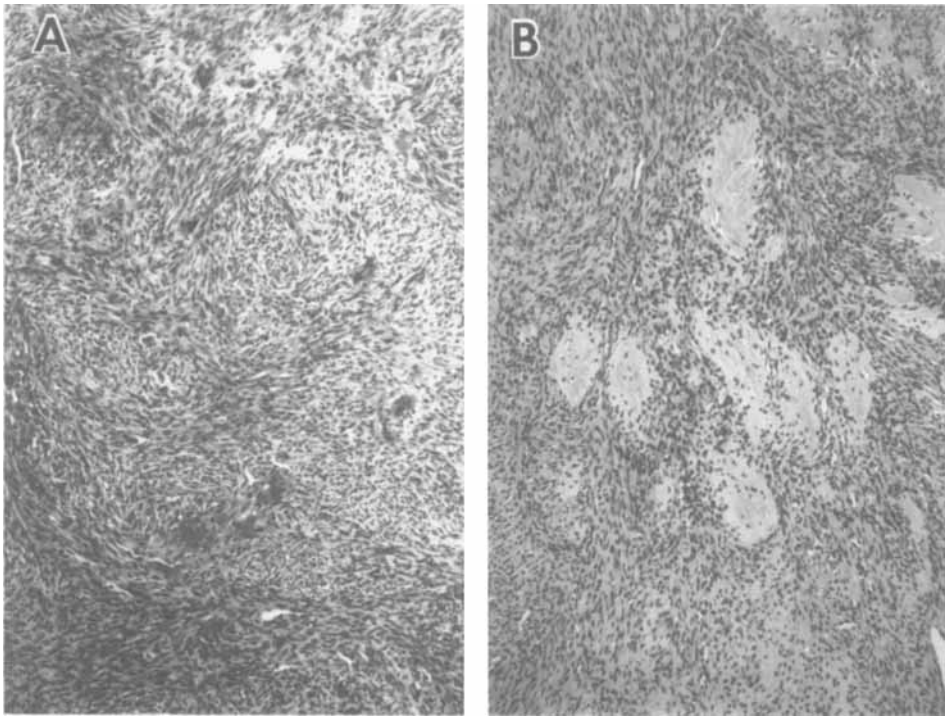
FIGS. 10A AND 10B. Case 12 (phosphaturic mesenchymal tumor, osteoblastoma-like variant). (A) Abundant sometimes confluent osteoid is shown composing most of the tumor stroma (H & E, original magnification ×5). (B) Highly vascular stroma is shown containing osteoclast-like giant cells adjacent to osteoid (H & E, original magnification ×100).

fying fibroma-like tumors (2 cases), and an ossifying fibroma-like tumor (1 case). Therefore, it appears that no single mesenchymal tumor having a homogeneous morphologic pattern causes all cases of oncogenic osteomalacia or rickets. However, the first and largest group of phosphaturic mesenchymal tumors having mixed connective tissue features appeared to be clearly unique and deserving of special mention.

These mixed connective tissue variants all contained variable numbers of primitive-appearing stromal cells



FIGS. 11A AND 11B. Case 12 (phosphaturic mesenchymal tumor, osteoblastoma-like variant). (A) Shown in greater detail are the cytologic features of the osteoblastic fibrous tissue. The spindle-shaped cells contain vesicular nuclei, prominent nucleoli, and moderate amounts of cytoplasm (H & E, original magnification ×250). (B) Histiocytic foam-cell nest is shown surrounding osteoid containing prominent osteoblastic rimming (H & E, original magnification ×62.5).



FIGS. 12A AND 12B. (A) Case 16 (phosphaturic mesenchymal tumor, nonossifying fibroma-like variant). Dense spindle-cell stroma containing scattered osteoclast-like giant cells and minimal vascularity (H & E, original magnification ×10). (B) Case 17 (phosphaturic mesenchymal tumor, ossifying fibroma-like variant). Spindle-cell stroma containing focal osteoid (H & E, original magnification ×10).

growing in poorly defined sheets. The tumor stroma was frequently microcystic and punctuated by clusters of osteoclast-like giant cells, sometimes associated with hemorrhage. Vascularity was often prominent and focally hemangiopericytoma-like in its growth pattern. In less-vascular areas the stroma sometimes appeared as poorly developed cartilage or contained foci of osteoid or bone. The poorly developed cartilage often displayed considerable dystrophic calcification. With the exception of one tumor, all tumors within this group occurred in soft tissues, displayed benign cytologic features, and behaved in a benign fashion. The single malignant example appeared to originate in bone, recurred locally, and metastasized to lung. This malignant tumor showed greater cytologic atypia and increased mitotic activity when compared to its benign counterparts. The patient remains alive, apparently with residual tumor, 6 years after initial diagnosis.[7]

Immunohistochemical studies of these peculiar mixed connective tissue variants (four cases)[1] have revealed only vimentin immunoreactivity, a feature of mesenchymal cells. All other reagents (including antibodies to desmin, S-100 protein, cytokeratin, leu-M1, chromogranin, leukocyte common antigen, Factor VIII-related antigen, neuron-specific enolase, and *Ulex europaeus 1*-lectin binding) have shown no evidence of epithelial, neural, vascular, or neuroendocrine differentiation in tumor cells. Even though the cartilage-like areas showed strong colloidal-iron staining both before and after hyaluronidase digestion, these areas were clearly S-100 protein negative. This observation suggests that these areas are not true cartilage, a tissue type usually S-100 protein positive. Ultrastructural studies (six tumors) have revealed osteoclast-like giant cells admixed with mesenchymal cells ranging from poorly differentiated polygonal cells with organelle-poor cytoplasm to fibrohistiocytic cells with organelle-rich cytoplasm. No neurosecretory granules were found. These studies only support the presence of mesenchymal differentiation in these tumors.

The diagnostic terminology for these primitive tumors remains controversial. Olefsky and co-workers[17] suggested "ossifying mesenchymal tumor associated with osteomalacia." Unfortunately not all tumors contain ossified areas, and it is sometimes difficult to differentiate reactive bone formation from true tumoral bone. Salassa and coworkers[4] suggested "sclerosing hemangioma," a term also favored by Mirra.[19] Other authors have used descriptive terms like "benign angiofibroma,"[5] "hemangiopericytoma,"[8] "chondrosarcoma,"[7] "primitive mesenchymal tumor,"[1] and "soft-parts chondroma-like tumor."[1] The diversity of these diagnostic labels underscores the morphologic complexity of these tumors and the difficulty in developing a single, universally acceptable term.

The tumor cell producing the putative phosphaturic substance remains unclear. However, primitive-appearing stromal cells were frequently observed in those tumors

studied by electron microscopy. In tumor 8 these cells were observed in close contact with osteoclast-like giant cells, and they contained occasional lipid vacuoles which could be acting as precursor reservoirs for a lipid or lipid-like hormone (or its precursors). In fact, similar lipid vacuoles are present in renal medullary interstitial cells and are thought to be reservoirs for antihypertensive renomedullary hormone or its precursors.[20] However, it is likely that not until the phosphaturic substance is isolated and characterized will it be possible to localize its production to a specific cell type.

Until the specific cell type or phosphaturic substance is characterized, we believe it is best to use a descriptive phrase to label these tumors. The diagnostic phrase we favor for the time being for those tumors occurring in soft tissues is "phosphaturic mesenchymal tumor (mixed connective tissue variant)." For those occurring in bone and resembling osteoblastomas we favor the phrase "phosphaturic mesenchymal tumor (osteoblastoma-like variant)," and so forth. Clearly, it is the production of the phosphaturic substance by these tumors that is the key to the pathogenesis of this fascinating syndrome. It is only a matter of time before examples of this tumor will be discovered early in the course of the disease (as they should be) when hypophosphatemia and phosphaturia are present without osteomalacia or rickets.

Why do tumors causing osteomalacia or rickets appear morphologically heterogeneous? With one exception all those examples with the morphology of the mixed connective tissue variant occurred in soft tissue. Possibly, when the mixed connective tissue variants occur in bone, the primitive-appearing cells are induced to differentiate and grow into tumors resembling osteoblastomas, nonossifying fibromas, or ossifying fibromas, while at the same time retaining the capacity to produce the phosphaturic substance. It is also possible that under certain circumstances, primary bone tumors or bone metastases (*e.g.*, prostate carcinoma)[21,22] induce surrounding bone tissue to secrete a phosphaturic substance. The answers to these questions will likely remain unknown until the phosphaturic substance or hormone is isolated and characterized. When that is achieved, we believe a great deal will be learned not only about the cause of oncogenic osteomalacia but also about phosphate homeostasis in general.

In summary, oncogenic osteomalacia or rickets should be suspected in any patient who presents with metabolic bone disease associated with hypophosphatemia and inappropriate phosphaturia. Serum 1,25-dihydroxyvitamin-D3 is low in nearly all cases, and serum alkaline phosphatase should be elevated. Once suspected, a vigorous and meticulous search for a small, inconspicuous tumor should be initiated. Obviously, once a suspicious mass in bone, skin, or soft tissue is discovered, it needs to be surgically removed and examined by a pathologist. The morphologic features of the tumor may help confirm the diagnosis of oncogenic osteomalacia or rickets, especially if it has the unique morphologic features of a phosphaturic mesenchymal tumor (mixed connective tissue variant). If a phosphaturic mesenchymal tumor is not found, one should consider other tumors that have been reported to cause oncogenic osteomalacia or rickets, such as prostate carcinoma, breast carcinoma, oat cell carcinoma, fibrous dysplasia, and soft tissue tumors occurring in neurofibromatosis.[1] Unfortunately, the causal role of tumor in many of these latter cases cannot be proven, because of the often extensive and unresectable nature of the lesions. It is also important to consider the possibility that a small phosphaturic mesenchymal tumor may exist concomitantly with one of these "other tumors." As a consequence, one should not forget to investigate these patients for an inconspicuous mesenchymal tumor as well. The dramatic cure of the osteomalacia or rickets that will result from tumor removal would be worth the effort and expense.

REFERENCES

1. Weidner N, Bar RS, Weiss D, Strottmann MP. Neoplastic pathology of oncogenic osteomalacia/rickets. *Cancer* 1985; 55:1691–1705.
2. Weiss D, Bar RS, Weidner N, Wener M, Lee F. Oncogenic osteomalacia: Strange tumours in strange places. *Postgrad Med J* 1985; 61: 349–355.
3. Moser CR, Fessel WJ. Rheumatic manifestations of hypophosphatemia. *Arch Intern Med* 1974; 134:674–678.
4. Salassa RM, Jowsey J, Arnaud CD. Hypophosphatemic osteomalacia associated with "neuroendocrine" tumors. *N Engl J Med* 1970; 282:65–70.
5. Cotton GE, Van Puffelen P. Hypophosphatemic osteomalacia secondary to neoplasia. *J Bone Joint Surg* 1986; 68:129–133.
6. Gitelis S, Ryan WG, Rosenberg AG, Templeton AC. Adult-onset hypophosphatemic osteomalacia secondary to neoplasm: A case report and review of the pathophysiology. *J Bone Joint Surg* 1986; 68:134–138.
7. Firth RG, Grant CS, Riggs BL. Development of hypercalcemic hyperparathyroidism after long-term phosphate supplementation in hypophosphatemic osteomalacia: Report of two cases. *Am J Med* 1985; 78:669–673.
8. Taylor HC, Santa Cruz D, Teitelbaum SL, Bergfeld M, Whyte MP. Oncogenic osteomalacia cured by resection of a unique soft tissue neoplasm: Assessment of calcitriol and phosphate therapy with detailed clinical investigation and histopathological study of tumor and bone (in preparation).
9. Yoshikawa S, Nakamura T, Takagi M, Imamura T, Okano K, Satoshi S. Benign osteoblastoma as a cause of osteomalacia: A report of two cases. *J Bone Joint Surg* 1977; 59:279–286.
10. Fukumoto Y, Seiichiro T, Keiko T *et al.* Tumor-induced vitamin D-resistant hypophosphatemic osteomalacia associated with proximal tubular dysfunction and 1,24-dihydroxyvitamin D deficiency. *J Clin Endocrinol Metab* 1979; 133:539–540.
11. Boriani S, Campanacci M. Osteoblastoma associated with osteomalacia (presentation of a case and review of the literature). *Ital J Orthop Traumatol* 1978; 4:379–382.
12. Pollack JA, Schiller AL, Crawford JD. Rickets and myopathy cured by removal of a nonossifying fibroma of bone. *Pediatrics* 1973; 52:364–371.

13. Asnes RS, Berdon WE, Basset A. Hypophosphatemic rickets in an adolescent cured by excision of a nonossifying fibroma. *Clin Pediatr* 1981; 20:646–648.

14. Nomura G, Koshino Y, Morimoto H, Kida H, Nomura S, Tamai K. Vitamin D resistant hypophosphatemic osteomalacia associated with osteosarcoma of the mandible: Report of a case. *Jpn J Med* 1981; 21: 35–39.

15. Taylor CR. Immunoperoxidase techniques: Practical and theoretical aspects. *Arch Pathol Lab Med* 1978; 102:113–121.

16. Churg J, Gerber MA. The processing and examination of renal biopsies. *Lab Med* 1979; 10:591–596.

17. Olefsky J, Kempson R, Jones H, Reaven G. "Tertiary" hyperparathyroidism and apparent "cure" of vitamin-D-resistant rickets after removal of an ossifying mesenchymal tumor of the pharynx. *N Engl J Med* 1972; 286:740–745.

18. Evans DJ, Azzopardi JG. Distinctive tumors of bone and soft tissue causing acquired vitamin-D-resistant osteomalacia. *Lancet* 1972; 1:353–354.

19. Mirra JM. Bone Tumors, Diagnosis, and Treatment, ed. 1. Philadelphia: J.B. Lippincott, 1980; 500–504.

20. Pitcock JA, Brown PS, Rapp JP, Crofton J, Muirhead EE. Morphometric studies of the renomedullary interstitial cells of Dahl hypertensive-prone and hypertensive-resistant rats. *Am J Pathol* 1982; 109: 123–128.

21. Lyles KW, Berry WR, Haussler M, Harrelson JM, Drezner MK. Hypophosphatemic osteomalacia: Association with prostate carcinoma. *Ann Intern Med* 1980; 93:275–278.

22. Charhon SA, Chapuy MC, Delvin EE, Valentin-Opran A, Edouard CM, Meunier PJ. Histomorphometric analysis of sclerotic bone metastases from prostatic carcinoma with special reference to osteomalacia. *Cancer* 1983; 51:918–924.