Phosphaturic mesenchymal tumors

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Tumors associated with oncogenic osteomalacia (OO) have a wide range of histopathological morphologies, and many clinicians and pathologists continue to be unaware of these diseases as a distinct entity.

Weidner and Cruz reviewed the literature of ~60 cases of OO that had been described at that time. They were the first to propose a classification system based on the histological findings of their 16 cases of OO, and named the tumors as phosphaturic mesenchymal tumors. These were then subdivided into four distinct morphological patterns: (i) primitive-appearing, mixed connective tissue tumors; (ii) osteoblastoma-like tumors; (iii) nonossifying fibroma-like tumors; and (iv) ossifying fibroma-like tumors. The first group, phosphaturic mesenchymal tumor, mixed connective tissue tumors (PMTMCT), consisted of neoplasias containing primitive stromal cells, prominent vessel, and osteoclast-like giant cells. Osseous metaplasia and poorly formed cartilage-like areas with dystrophic calcification were also noted. They presented that these tumors usually occurred in the soft tissue and were typically benign in nature. The remaining three groups tended to occur in bone and were also typically benign in nature. In 1994, Park et al. reviewed 17 OO 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. Folpe et al. reviewed the clinic-pathological features of 32 new cases and re-reviewed previously published cases, and made the assertion that virtually all of the cases fell into the category of PMTMCT. Currently the prototypical phosphaturic mesenchymal tumor (mixed connective tissue variant) (PMTMCT) contains
neoplastic cells that are spindled to stellate in shape, normochromatic with small nuclei and indistinct nucleoli. The nuclear grade is low, and mitotic rate is usually absent or very low. The cells are typically embedded within a myxoid or myxochondroid matrix with “grungy” calcification that can resemble chondroid or osteoid. Numerous osteoclast-like giant cells are a frequent histological findings, and mature fat and even lamellar bone may be present. A prominent, characteristic finding of these tumors is an elaborate intrinsic microvasculature with an admixture of vessel size and vascular pattern. The most common diagnosis for these tumors has been hemangiopericytoma, but it also included hemangioma, sarcomas, ossifying fibromas, granulomas, giant cell tumors and osteoblastomas.

Antigen expression was first evaluated in two immunohistochemical studies by Weidner et al. In the first study, the immunostaining were negative for FVIII-related antigen, S-100 protein, and cytokeratin. The second study demonstrated only vimentin immunoreactivity in some cases within the tumor cells. All other antibodies (desmin, S-100 protein, Leu-M1, chromogranin, cytokeratin, neurom-specific enolase, leukocyte common antigen, and factor VIII-related antigen) were negative. In their series, Folpe et al. performed a series of immunohistochemical stainings, including pan-cytokeratin, desmin, S-100, smooth muscle actin, CD34, and FGF23. With the exception of smooth muscle actin, which they found reactive in three cases, and FGF23, which was positive in about 70% of all the cases studied. All other markers were negative. In terms of FGF23 staining, it is the proliferating cells within the tumor that usually stain positive for FGF23. In 2004, Toyosawa et al. performed immunostaining using dentin matrix protein 1 (DMP 1) in OO. DMP1 expression was observed in all of the three cases with PMTMCT and detected in the extracellular matrix with myxomatous features around capillary vessels and in dystrophic calcified sites. Recently Hannan et al. performed immunostaining using lymphatic vessel endothelial hyaluronan receptor 1 (LYVE-1) to verify lymphatic vessels in the PMYMCT and demonstrated lymphatic vessels, it might be helpful to distinguish these tumors from the typical benign hemangiomas. Imanishi et al. performed immunostaining in 11 cases of PMTMCT using matrix extracellular phosphoglycoprotein (MEPE) and revealed that MEPE was expressed in 10 out of 11 cases of OO.

Tumor induced osteomalacia, also known as oncogenic osteomalacia is a rare paraneoplastic syndrome of abnormal phosphate and vitamin D metabolism caused by typically small endocrine tumors that secrete phosphaturic substances, such as fibroblast
growth factor 23 (FGF23). Biochemical hallmarks of the disorder are hypophosphatemia due to renal phosphate wasting, inappropriate normal or low 1,25 dihydroxyvitamin D, and elevated or inappropriate normal plasma FGF23. Robert McCance (1947) is often named with the first reported case of OO. McCance reported a patient with manifestations of what was clearly OO. The patient had pain, weakness, gait abnormalities, and low phosphorus levels. She was treated with high dose of vitamin D, but her symptoms did not completely recovered until a tumor in her femur was resected. The first person to clearly understand that the disease was the result of a ‘rachitogenic’ substance was Andrea Prader. In 1959, he described an 11 1/2-year-old girl who developed severe rickets over the course of a year. Evaluation showed decreased tubular phosphate reabsorption but otherwise normal kidney function. A tumor, classified as a giant cell granuloma, was identified in a rib and resected with subsequently healing of her rickets. Prader highlighted the association between the resection of the tumor and the cure of the rickets and posited that the granuloma was secreting a rachitogenic substance.

The pathophysiologic basis underlying OO remains unknown. Most researchers agree that tumor production of a humoral substance, phosphatonin that may affect multiple functions of the proximal renal tubule, particularly phosphate reabsorption (resulting in hypophosphatemia), is the probable pathogenesis of OO. One of the known phosphatonins is fibroblast growth factor 23 (FGF23).

The FGF23 gene, which resides on human chromosome 12p13 (mouse chromosome 6), is comprised of three coding exons and contains an open reading frame of 251 residues. The tissue with the highest FGF23 expression is bone, and FGF23 mRNA is observed in osteoblasts, osteocytes, flattened bone lining cells, and osteoprogenitor cells. FGF23 reduces renal Pi reabsorption but has opposite effects on 1,25(OH)2D. FGF23 acts by binding to target cells via an FGF receptor, but signaling requires the co-receptor Klotho. The two primary transport proteins responsible for Pi reabsorption in the kidney are the type II sodium-phosphate co-transporters, NPT2a and NPT2c, expressed in the apical membrane of the proximal tubule. When FGFR is activated, there is reduction of NaPi-2a transcription and less NaPi-2a on the basal cell surface of proximal tubular cells, which in turn leads to renal phosphate excretion.

MEPE is also called osteoblast/osteocyte factor 45, as it is mainly expressed in
osteoblasts and osteocytes and was first identified in a cDNA library of OO. The MEPE gene encodes a 525-amino acid extracellular matrix protein. MEPE shares a sequence homology with the small integrin binding ligand, N-linked glycoprotein (SIBLING) family protein such as bone sialoprotein, dentin sailophosphoprotein, osteopontin, and the dentin matrix protein; all of which are clustered on chromosome 4q21 in humans and chromosome 5q in mice. The C-terminal acidic serine aspirate rich MEPE (ASARM) motif of the MEPE protein can be cleaved by proteolytic activity of cathepsin B. The proteolytic cleavage is protected by another enzyme, PHEX. The released ASARM motif circulates in the bloodstream to regulate reabsorption of phosphate in the renal proximal tubules and mineralization of the bones and teeth. For this reason, ASARM peptide is also called minhibin due to its bone mineralization-inhibiting action and phosphatonin due to its phosphate reabsorption-inhibiting action.

DMP1 is a member of the SIBLING family, a group of non-collagenous extracellular matrix proteins involved in bone mineralization. These genes are localized to human chromosome 4q21-25. They have similar exon arrangements and include dentin sialoprotein, dentin phosphoprotein, osteopontin, integrin-binding sialoprotein, and matrix extracellular phosphoglycoprotein. DMP1 is highly expressed in osteocytes and is comprised of 513 residues, but is secreted in bone and dentin as 37 kDa N-terminal and 57 kDa C-terminal fragments from a 94 kDa full-length precursor. Potential roles for DMP1 in bone may include regulating hydroxyapatite formation, and depending upon proteolytic processing and phosphorylation, it may regulate local mineralization processes in vivo. In autosomal recessive hereditary rickets, the DMP1 gene is lost and subsequently causes impaired osteocyte differentiation and increased production of FGF23.

To summarize, PMTMCT are a group of tumors with a wide spectrum of histopathological findings that include a background of spindle/stellate cells with low nuclear and mitotic activity. Prominent hemangiopericytic vascularity is common and some other features include different sizes and patterns. Osteoclast-like giant cells are frequently present in most of the tumors. FGF23 staining is positive and appears in the cytoplasm of the tumor cells. The first and foremost treatment of OO is complete resection of the associate tumor. However, recurrence of mesenchymal tumors, such as giant cell tumors of bone, or the inability of complete resection of certain malignancies, such as prostatic carcinoma, has resulted in the need for therapeutic intervention.
References

1. McCance RA: Osteomalacia with looser’s nodes (milkman’s syndrome) due to a raised resistance to vitamin D acquired about the age of 15 years. Q J Med 16:33-46, 1947


