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# The Paraneoplastic Presence-Phosphaturic Mesenchymal Tumor

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## Abstract

Phosphaturic mesenchymal tumor is a unique neoplasm of bone and soft tissue delineating diverse, specific histological features along with production of FGF-23 and associated metabolic bone defects such as rickets and osteomalacia. Paraneoplastic syndrome engendered by the neoplasm is associated with an acquired variant of Oncogenic Osteomalacia (OO), which can also appear in diverse mesenchymal neoplasia. Reoccurring tumefaction with Oncogenic Osteomalacia (OO) can emerge within sites such as mandible along with pulmonary and soft tissue metastasis. Although the neoplasm can delineate intermediate malignant potential and unpredictable biological behaviour, distant metastasis is exceptional. Phosphaturic mesenchymal tumor was initially described by Mc Cane in 1947 with subsequent concordance between the neoplasm and osteomalacia. Subsequently, Weidner and Cruz denominated the terminology of "Phosphaturic Mesenchymal Tumor" (PMT) in 1987, adequately describing the morphological characteristics. Although osteomalacia is manifest, phosphaturic mesenchymal tumor can be histologically misinterpreted. Occurrence of phosphaturic mesenchymal tumor in young individuals with skeletal deformities requires a distinction from disorders such as rickets or vitamin D deficiency. Elderly individuals depicting incrimination of ribs or multiple vertebral bodies may be indicative of multiple myeloma.

**Keywords:** Hot pepper; Management option; Vectors; Viruses

## Introduction

Phosphaturic mesenchymal tumour is a unique neoplasm of bone and soft tissue delineating diverse, specific histological features along with production of FGF-23 and associated metabolic bone defects such as rickets and osteomalacia. Paraneoplastic syndrome engendered by the neoplasm is associated with an acquired variant of oncogenic osteomalacia (OO), which can also appear in diverse mesenchymal neoplasia. Reoccurring tumefaction with oncogenic osteomalacia (OO) can emerge within sites such as mandible along with pulmonary and soft tissue metastasis. Although the neoplasm can delineate intermediate malignant potential and unpredictable biological behaviour, distant metastasis is exceptional. Phosphaturic mesenchymal tumour was initially described by Mc Cane in 1947 with subsequent concordance between the neoplasm and osteomalacia [1]. Subsequently, Weidner and Cruz denominated the terminology of "Phosphaturic Mesenchymal Tumour" (PMT) in 1987, adequately describing the morphological characteristics [2]. Although osteomalacia is manifest, phosphaturic mesenchymal tumour can be histologically misinterpreted. Occurrence of phosphaturic mesenchymal tumour in young individuals with skeletal deformities requires a distinction from disorders such as rickets or vitamin D deficiency. Elderly individuals depicting incrimination of ribs or multiple vertebral bodies may be indicative of multiple myeloma.

## Disease Characteristics

Although phosphaturic mesenchymal tumor can arise anywhere within the bone or soft tissue, appendicular skeleton and extremities (95%) are commonly implicated whereas head and neck (5%) lesions are exceptional. Within the head and neck, tumor localization is discerned within sino-nasal cavity (57%) followed by mandible (20%) [3]. Also, lesions can emerge within chest wall, pharynx, maxilla, tongue, breast, spine, floor of mouth and posterior neck. Extra oral tumefaction is frequent in females with a female to male proportion of 2:1. Intraoral tumor's delineate a mild male predominance. Tumors arising within hard and soft tissue are equivalently distributed with a slight predilection of bony sites, such as distal radius. Median age of disease representation is 45 years whereas the condition is commonly discerned between 24 years to 58 years, although young subjects can be incriminated and no age of disease occurrence is exempt. A slight female predilection is observed with female to male ratio

 

of ~1.7:1. Specific factors of probable disease emergence are absent. Tumefaction is miniature and gradually progressive, thus several or a mean of 5 years is necessitated for adequate tumor localization. Incidence of phosphaturic mesenchymal tumor arising within head and neck may be enhanced as the neoplasm is frequently misinterpreted as glomangiopericytoma, giant cell tumor or low grade osteosarcoma. Phosphaturic mesenchymal tumor comprises of majority (80%) of mesenchymal neoplasms engendering Oncogenic Osteomalacia (OO) whereas around 20% of osteomalacia associated neoplasms are adjunctive mesenchymal tumefaction such as haemangiopericytoma, giant cell tumor of bone, osteosarcoma, fibrous dysplasia, aneurysmal bone cyst or chondromyxoidfibroma. Phosphaturic mesenchymal tumor produces Fibroblast Growth Factor-2 (FGF-2), a protein which inhibits reabsorption of phosphate or dentin matrix protein 1 by renal tubules. An estimated 60% neoplasms arising within non head and neck sites can harbour a chromosomal translocation with production of contemporary FN1-FGFR1 fusion protein, which engenders an upregulation of FGFR1 receptor. Majority of phosphaturic mesenchymal tumors are benign whereas an estimated 10% neoplasms relapse. Malignant metamorphosis is accompanied with multifocal or metastatic disease. Multiple, miniature, non-obstructive foci of pulmonary tumor metastasis can be discerned following repetitive surgeries. Malignant neoplasms can metastasize to nasal cavity, lip or tongue [3,4].

## Disease pathogenesis

The neoplasm frequently engenders Tumor Induced Osteomalacia (TIO) which is a paraneoplastic syndrome characteristically delineating phosphate wasting within renal tubules with subsequent hypophosphatemia [4]. Osteomalacia is an adult metabolic disorder incorporating mineralization of mature bone and is generated by vitamin D deficiency, various medications, malabsorption, hepatic or renal disorders. Oncogenic Osteomalacia (OO) is an exceptional clinico-pathological condition of acquired, secondary osteomalacia arising due to phosphaturic mesenchymal tumor. Phosphaturic mesenchymal tumor induces renal phosphate decimation with consequent osteomalacia via production and secretion of phosphatonins, commonly Fibroblast Growth Factor 23 (FGF-23). Phosphatonins circumvent reabsorption of phosphate within proximal renal tubules with resultant hypophosphatemia and subsequent bone depletion. Overexpression of FGF-23 is accompanied by Fibronectin-1-Fibroblast Growth Factor -1 (FN1-FGFR1) fusion, as discerned by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR), a feature which is manifest in a subset of neoplasms. As FN1-FGFR1 fusion gene is discerned in around 60% of neoplasms, it is posited to be the pathway of tumori-genesis [4,5]. A subset of phosphaturic mesenchymal tumors arising within head and neck harbour FGFR1 chromosomal translocation, an anomaly which can be adequately discerned with Fluorescent *In Situ* Hybridization (FISH), beneficially adopted in instances of obscure clinical and laboratory manifestations. Biochemical assay delineates enhanced bone turnover with hypophosphatemia, hyper-phosphaturia, elevated alkaline phosphatase, normal to minimal circulating levels of 1, 25-dihydroxy-vitamin D3 (1,25-[OH]2D3), normal serum calcium and Parathyroid Hormone (PTH), findings which are consistent with Oncogenic Osteomalacia (OO) [5]. Phosphate imbalance arises due to excessive expression of phosphatonin or Fibroblast Growth Factor 23 (FGF-23), an ectopic, hormone-like protein secreted by phosphaturic mesenchymal tumor. Enhanced levels of FGF-23 engender phosphate diuresis or phosphaturia which prohibits reabsorption of renal phosphate with consequent hypophosphatemia. Aforesaid manoeuver activates the mobilization of phosphate and calcium from bone into circulating blood as a compensatory mechanism with weakening of bones and consequent fractures. Thus, enhanced expression of FGF-23 is contemplated to be diagnostic of phosphaturic mesenchymal tumor. As FGF-23 inhibits transportation and reabsorption of phosphate within proximal renal tubules, metabolism of vitamin D is influenced with circumvention of conversion of 25-hydroxy-vitamin D to 1,25-dihydroxy vitamin D. Although precise mechanism of FGF-23 influencing phosphate equilibrium is obscure, it's function is separate from type-II a sodium phosphate co-transporter (NaPi-2a), a molecule which is regulated by Parathyroid Hormone (PTH) and significantly constitutes towards renal phosphate reabsorption. Additionally, heparin- like molecules and Mitogen-Activated Protein Kinase (MAPK) pathway may be pertinent for activity of FGF-23 [5,6].

## Clinical features

The neoplasm is subdivided into four distinct categories as phosphaturic mesenchymal tumor mixed connective tissue type which occurs within soft tissue osteoblastoma-like ossifying fibroma-like, non-ossifying fibroma-like. Aforesaid categories are discerned within diverse bony sites. Bone and soft tissue lesions appear as a singular entity or as components of a wide histological spectrum. A subset of tumors may not demonstrate phosphate diuresis and are labelled as non phosphaturic variant of phosphaturic mesenchymal tumor. Clinical representation is contingent to anatomic distribution of lesions and is manifest by bone pain, multiple bone fractures, muscle tenderness, anomalies of gait, atrophy of proximal muscles and osteopenia. Typically, pain and weakness is denominated. Numerous pathologic fractures within the spine, ribs, sacrum or calcaneus can appear. Destructive, osteolytic lesions can arise within incriminated bones. Adolescent subjects can depict rickets-like skeletal deformities. Symptoms of hypophosphatemia or osteomalacia can ensue with chronic pain or pathological fractures. Tumor discernment can be challenging in individuals demonstrating an absence of osteomalacia. Subjects can exhibit chronic lumbar pain with osteopenia of lumbar spine and neck of femur, osteoporosis of diverse bones as distal third of radius and history of atraumatic rib fractures [5,6]. Clinical symptoms are pertinent to implicated tumor site. Also, osteomalacia may not a comprehensive clinical feature. The neoplasm may not be clinically evident at representation and discernment is often delayed. Thus, incriminated subjects can be preliminarily treated for hypophosphatemia and osteoporosis [6]. On examination, dome shaped, symmetrical, non-ulcerated lesions of varying magnitude at intra-oral or diverse sites can be discerned. Phosphaturic mesenchymal tumor can be devoid of

accompanying Tumor Induced Osteomalacia (TIO) and manifest normal serum phosphate levels at initial disease representation. Tumor localization with early disease onset, prior to appearance of TIO is pertinent in aforesaid instances.

### Histological elucidation

The mesenchymal, soft tissue or bony, variably cellular neoplasm with an infiltrative perimeter characteristically demonstrates foci of pale grey, flocculent or "grungy" calcification. Tumor magnitude varies from 2 centimetres to 14 centimetres. Infiltrative, hypo-cellular tumefaction is composed of spindle-shaped cells, irregular or miniature foci of "grungy" or flocculent calcification and an encompassing chondromyxoid or osteoid- like matrix with plump, fibroblastic cells [6]. Characteristically, proliferating spindle-shaped cells are intermixed with several pseudo-vascular spaces and calcified tumor matrix. Well defined, spindle-shaped, stellate or epithelioid cells with intermixed multinucleated giant cells and circumscribing chondromyxoid matrix denominate the neoplasm. Focal micro-mineralization envelops individual tumor cell. Singular, cellular subtype can predominate in a specific neoplasm. Zones of flocculent or "grungy" calcification are interspersed within tumor cells [6,7]. Uniform, spindle- shaped cells are benign appearing and demonstrate miniature nuclei, well dispersed nuclear chromatin and indistinct nucleoli. Haemagiopericytoma-like vascular pattern, distinct foci of "grungy" calcified matrix, mature adipose tissue, focal microcyst formation, haemorrhage, an incomplete perimeter of membranous ossification and zones of metaplastic bone formation are discerned. Osteoid-like matrix or spindle-shaped cellular proliferation can occasionally display an absence of multinucleated giant cells or calcification. Thus, tumor discernment in aforesaid instances is challenging. Infiltrative, storiform or fascicular tumor pattern can be observed. Mitotic activity is minimal to absent. Tumor is devoid of atypia. As the significantly vascular neoplasm is characteristically configured by uniform, spindle-shaped cells and numerous, disseminated multinucleated giant cells enveloped within a chondromyxoid matrix with focal calcification, stromal alterations may vary from myxoid to hyalinised to abundantly collagenous to zones of osteoid-like matrix, admixed punctate or flocculent calcification. Extensively cellular neoplasm exemplifies numerous, osteoclast –like, multinucleated giant cells. Neighbouring vascular articulations are thin walled and impart a sieve-like appearance to the tumefaction. Foci of red cell extravasation are observed. Enhanced tumor cellularity, hyperchromasia or significant cellular pleomorphism is discerned. Cellular neoplasm configured of spindle-shaped cells and osteoid-like matrix is designated as an "ossifying" subtype of phosphaturic mesenchymal tumor. Extensive metastatic disease can ensue in advanced cases with mitotic activity ranging from 10 to 25 per 10 high power fields. Aggressive or metastatic tumefaction delineates a proliferative index Ki67 of around ˜3%. Malignant metamorphoses of phosphaturic mesenchymal tumor is exceptional and challenging to discern as tumor expanses may resemble undifferentiated pleomorphic sarcoma or malignant fibrous histiocytoma. Malignant conversion is exhibited by nuclear atypia, mitotic figures exceeding >5 per 10 high power fields and enhanced tumor cellularity. Cytological features of the neoplasm may not be predictive of malignant biological behaviour. On cytogenetic analysis, an FGFR1 chromosomal translocation is identified in around 80% of tumor cells. Also, complex chromosomal translocations can occur in nearly 42% of cells [7] (Figures 1-8).

## Immune histochemical elucidation

Phosphaturic mesenchymal tumor is immune reactive to vimentin, thereby indicating a mesenchymal origin. Additionally, the neoplasm is immune reactive to Fibroblast Growth Factor 23 (FGF-23) and dentin matrix protein1 and is immune non-reactive to S100 protein, CD68, CD34, desmin or cytokeratin.

## Differential diagnosis

Phosphaturic mesenchymal tumor requires a segregation from cementifying fibroma, myxoid neoplasm, benign

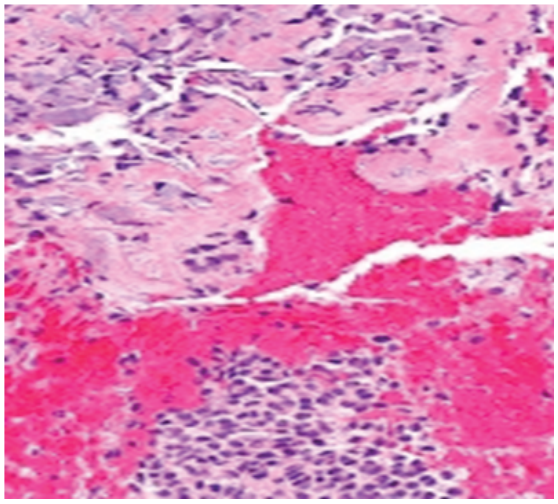

**Figure 1** Phosphaturic mesenchymal tumor delineating spindled-shaped cellular neoplasm with extensive areas of red cell extravasation and an encompassing collagenous stroma.

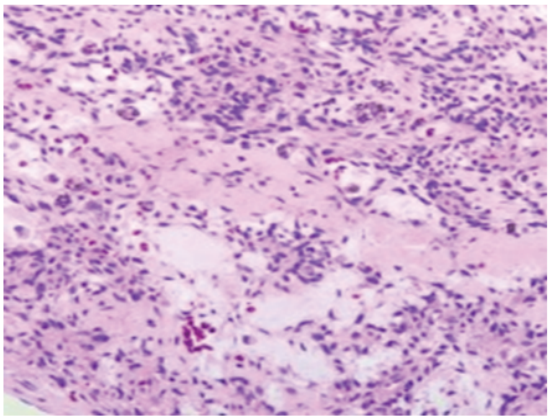

**Figure 2** Phosphaturic mesenchymal tumor exhibiting spindle-shaped and epithelioid cells embedded within a collagenous stroma and occasional multinucleated giant cells.

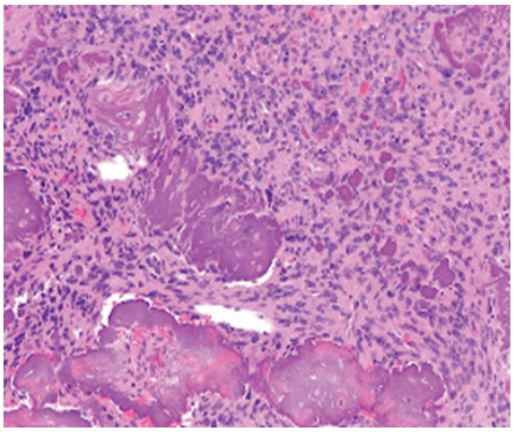

**Figure 3** Phosphaturic mesenchymal tumor elucidating abundant spindle-shaped cells intermixed with multinucleated giant cells and enveloping collagenous stroma with focal calcification. (Image 3 Courtesy: Twitter).

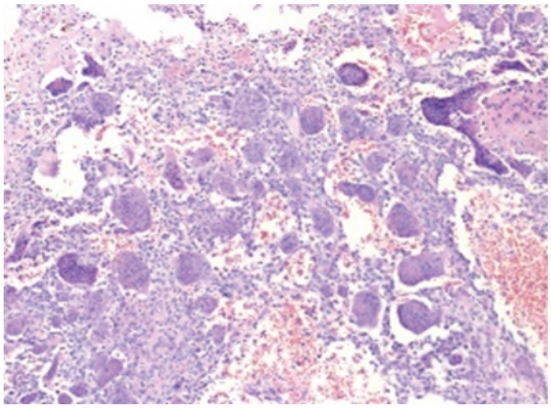

**Figure 4** Phosphaturic mesenchymal tumor exemplifying epithelioid cells admixed with foci of grungy calcification and a collagenous stroma.

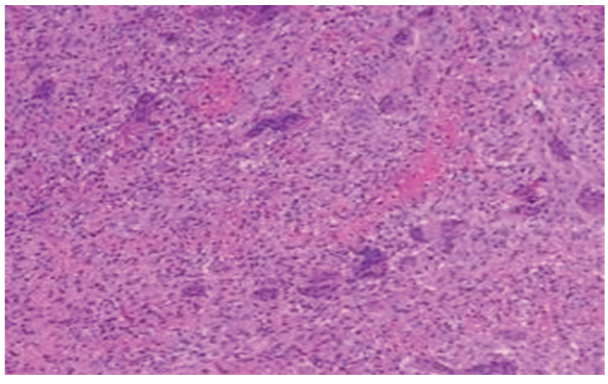

**Figure 5** Phosphaturic mesenchymal tumor exhibiting dense aggregates of spindle-shaped cells commingled with flocculent calcification and collagenous stroma.

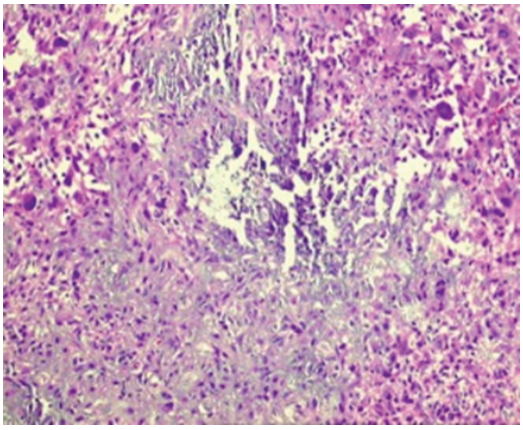

**Figure 6** Phosphaturic mesenchymal tumor delineating spindle-shaped and epithelioid tumor cells intermixed with flocculent calcification and circumscribing collagen-rich stroma.

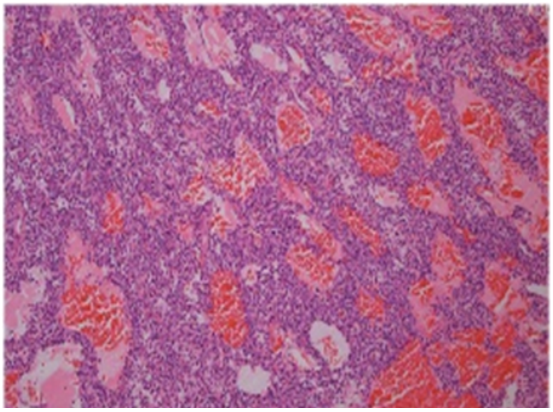

**Figure 7** Phosphaturic mesenchymal tumor demonstrating neoplastic spindle-shaped cells admixed with a collagenous stroma and extensive areas of red cell extravasation.

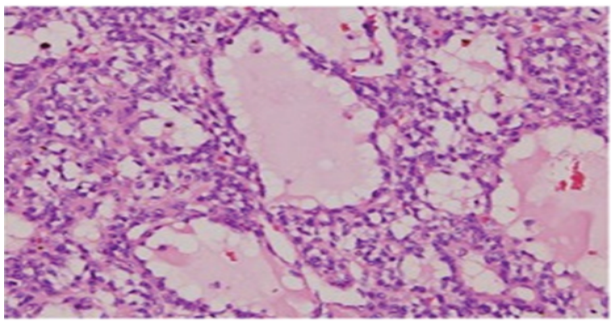

**Figure 8** Phosphaturic mesenchymal tumor depicting aggregates of spindle-shaped cells intermingled within a collagenous stroma and foci of flocculent calcification

chondromesenchymal tumor and giant cell tumor of soft tissue. Soft tissue neoplasms necessitating distinction are Solitary Fibrous Tumor (SFT) and glomangiopericytoma, tumors which recapitulate the vascular configuration of phosphaturic mesenchymal tumor although lack chondromyxoid matrix and "grungy" or flocculent calcification. Bone tumors mandating demarcation are giant cell tumor, chondromyxoid fibroma, chondroma and chordoma [8]. Mesenchymal neoplasms engendering Oncogenic Osteomalacia (OO) are haemangiopericytoma, giant cell tumor of bone and osteosarcoma. Giant cell tumor is characterized by proliferation of mononuclear and osteoclast-like giant cells, demonstrating identical nuclear features. Giant cell tumor of bone demonstrates numerous multinucleated giant cells composed of clear cytoplasm and an agglomeration of roughly 20 nuclei to 25 nuclei. Foci of spindle-shaped cells, typically configuring a storiform pattern and reactive, immature bone is delineated although chondroid matrix of phophaturic mesenchymal tumor is absent, which contains fewer multinucleated giant cells with fewer nuclei. Chondromyxoid fibroma is a lobulated, well circumscribed lesion comprised of chondroblasts imbued with abundant, eosinophilic cytoplasm. Tumor cells are embedded within a myxoid or poorly configured, hyalinised, cartilaginous stroma. Periphery of tumor nodules delineated enhanced cellularity. Osteoclasts, zones of calcification and spindle-shaped cells are typically exhibited within fibrous septa. Although tumor vascularity is enhanced, blood vessels are disparate from haemangiopericytoma-like vascular configurations of phosphaturic mesenchymal tumor. Chordoma is an exceptional, malignant bone tumor which arises from midline of foetal notochord. Dual cellular categories comprising the neoplasm are elliptical cells and physaliferous cells articulating cords and lobules, separated by fibrous tissue septa. Neoplastic cells are enmeshed within an extensively myxoid stroma with foci of calcification and accumulated multinucleated giant cells. However, predominant spindle-shaped cellular component is lacking. Chordoma is immune reactive to S100 protein, cytokeratin, Epithelial Membrane Antigen (EMA) and brachury. Cementifying fibroma is discerned within mandible, maxilla or adjunctive facial bones and is a well circumscribed neoplasm containing variable quantities of mineralized matrix simulating cementum. The neoplasm is composed of bland, spindle-shaped cells with foci of calcification, akin to phosphaturic mesenchymal neoplasm [8,9]. Haemangiopericytoma displays hyalinised, "staghorn" blood vessels layered by spherical to elliptical cells. Tumefaction lacks "grungy", flocculent calcification and tumor associated multinucleated giant cells. Osteosarcoma histologically simulates phosphaturic mesenchymal tumor, engenders variable quantities of bone or neoplastic osteoid directly from tumor cells and displays cytological atypia. The neoplasm can manifest a significant cartilaginous component. In contrast, phosphaturic mesenchymal tumor is composed of bland, spindle-shaped cells although bone is also generated. As osteosarcoma or chondrosarcoma require segregation, typical foci of phosphaturic mesenchymal tumor necessitate recognition and aid differentiation.

## Investigative assay

Preoperative biochemical analysis can exhibit hypo-phosphatemic syndrome concurrent with Tumor Induced Osteomalacia (TIO) and consequent hyperphosphaturia. Enhanced expression of FGF-23 m RNA within neoplastic cells can be demonstrated by Chromogenic *In Situ* Hybridization (CISH), efficaciously employed upon formalin fixed, paraffin embedded tissue. Molecular assay of serum FGF-23 can be beneficially adopted. Contemporary FN1-FGFR1 fusion protein, which engenders an upregulation of FGFR1 receptor, can be discerned by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR), Fluorescent In Situ Hybridization (FISH) or Western blot analysis [9]. However, FGFR1 gene can demonstrate an alternative chromosomal translocation pattern which requires the adoption of multiple sequence specific probes, as discerned by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR). Break apart fluorescent in situ hybridization (FISH) assay can delineate chromosomal translocation of FGFR1 gene with associated partner genes. Subjects with TIO can manifest histological features concurrent with phosphaturic mesenchymal tumor and associated head and neck neoplasms such as glomangiopericytoma. Aforesaid tumors warrant adequate discernment with ancillary molecular techniques such as Fluorescent *In Situ* Hybridization (FISH), which can confirm chromosomal translocation within FGFR1 gene or Chromogenic In Situ Hybridization (CISH), in order to delineate elevated expression of FGF-23. In Situ hybridization performed for FGF-23 demonstrates a diffuse, intense cytoplasmic staining. Aforesaid procedures can be performed on formalin fixed, paraffin embedded tissue. Occasionally, appropriate detection of miniature tumors can be challenging. Therefore, cogent methods of assessment such as Magnetic Resonance Imaging (MRI), octreotide scintigraphy and Positron Emission Computerized Tomography (PET-CT) can be suitably adopted. Cogent factors in disease discernment are age and gender of incriminated individual, tumor localization, initial diagnosis, duration of symptoms, occurrence of Tumor Induced Osteomalacia (TIO) with serum calcium and phosphate levels [9].

## Therapeutic options

Subjects with extensive Tumor Induced Osteomalacia (TIO) exceeding >10 years are initially managed with supplemental phosphate. Eventually, surgical resection of the neoplasm is curative and alleviates hypophosphatemia. Adequate surgical eradication of the neoplasm with a broad perimeter of tumor-free tissue is a preferred mode of therapy. Elevated serum phosphate can occur within weeks following surgery, levels which can return to normal with pertinent surgical excision. Surgical eradication can suitably reverse metabolic effects engendered by the neoplasm. Tumor reoccurrence is absent. Also, clinical behaviour of the neoplasm is unpredictable and lacks concurrence with manifested cytological features. Thus, extended follow up is warranted. Neoadjuvant chemotherapy can be concomitantly adopted with extensive surgical extermination, especially with metastatic disease. Adjunctive treatment strategies such as

radiotherapy and chemotherapy can be contemplated for treating tumefaction unamenable to surgery.

## Conclusion

Phosphaturic mesenchymal tumour is associated with enhanced bone turnover, hypophosphatemia, hyper-phosphaturia, elevated alkaline phosphatase along with normal to minimal circulating levels of 1,25 dihydroxy-vitamin D3 (1,25-[OH]2D3), normal serum calcium and parathyroid hormone (PTH), consistent with oncogenic osteomalacia. The neoplasm is immune reactive to vimentin, fibroblast growth factor 23 (FGF-23) and dentin matrix protein1. Phosphaturic mesenchymal tumour requires a segregation from cementifying fibroma, myxoid neoplasms, benign chondromesenchymal tumour, giant cell tumour of soft tissue, solitary fibrous tumour (SFT), chordoma, glomangiopericytoma, haemangiopericytoma, chondromyxoid fibroma and osteosarcoma. Enhanced expression of FGF-23 mRNA within neoplastic cells is demonstrated by Chromogenic In Situ Hybridization (CISH). Contemporary FN1-FGFR1 fusion protein is discerned by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR), Fluorescent In Situ Hybridization (FISH) or Western blot analysis. Magnetic Resonance Imaging (MRI), octreotide scintigraphy and Positron Emission Computerized Tomography (PET-CT) can be suitably adopted to evaluate miniature neoplasms. Adequate surgical eradication of the tumefaction with a broad perimeter of tumour-free tissue is an optimal treatment strategy.

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