Tumor Induced Osteomalacia

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Objective: *Tumor induced Osteomalacia (TIO) is a rare paraneoplastic syndrome which mostly caused by mesenchymal cell tumors that secrete a phosphaturic hormone called fibroblast growth factor-23 (FGF-23). These FGF-23-secreting tumors have its uniqueness of being a small tumor which are deep-seated inside patient's body and they are very difficult to be located. This report is about an epidural mesenchymal tumor adjacent to 6th thoracic vertebrae.*

Method: *To locate the culprit tumor using thorough physical examination, clinical radiographs with functional imaging and laboratory investigations in a 71-year-old female patient presented to our office with TIO.*

Result: *A 71-year-old female came with chief complaints of moderate body pains, muscle weakness and increasing thoracic kyphosis in 2 years. Laboratory investigation shows hypophosphatemia. Plain radiographs found pseudofracture of distal phalanx of her right thumb without any history of trauma. Parathyroid scan (MIBI + Pertechetate) shows an enhancing nodule measuring about 0.5×1.1 cm locate at lower pole of right parathyroid gland with further imaging of MRI Neck and Thorax found an epidural elongated mass measuring about 0.8×1.3×2 cm adjacent to 6th thoracic vertebrae. By the 6th day after tumor removal, serum phosphorus level reached normal range. Patient's symptoms were improved without phosphorus supplements. Histological reports show its cell type as spindle cell tumor.*

Conclusion: *TIO is body conditions response from over-regulated FGF-23 secretion of small soft tissue tumor. which very difficult to be located. Once complete tumor resection is done, TIO will be complete cured.*

Keywords: *TIO, Osteomalacia, FGF-23*

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Introduction

Tumor induced Osteomalacia is a rare paraneoplastic syndrome with its common symptoms including muscle pain, muscle weakness and pseudofractures. All TIO associate with FGF-23 producing tumor. Circulating FGF-23 can cause hypophosphatemia via phosphorus wasting. TIO was first reported in 1947 by McCance[(1)]. Since then most of these tumors are benign mesenchymal tumors but there are reports of malignancy[(2)] secreting FGF-23. This case report presents a senile female with clinical features of osteomalacia caused by a hidden epidural tumor.

Case Report

A 71 years old woman came with chronic body pain for 6 years with leg muscle weakness and trouble walking. There is no history of fever with peripheral joint swelling. Physical examination reveals stooping posture. Physical examination of other body system examination was unremarkable.

First laboratory test found serum calcium 9.7 mg/dl (8.0 -0.2), phosphorus level 1. mg/dl (2.5 - 4.5), alkaline phosphatase 256 U/L (35 - 104), 25-hydroxyvitamin D 22.62 ng/ml (20 - 100 ng/ml), parathyroid hormone level 139 pg/ml (15 - 65). Renal functions and serum electrolytes are normal. The level of FGF-23, assessed by Enzyme-linked immunosorbent assay (ELISA) was high. (188 pg/mL; normal range 8.2-54.3 pg/mL)

During work up the location of tumor, the patient was received calciferol 20,000IU 2 tabs/week, calcium carbonate 1,000 mg/day, but the patient was refused to take a phosphate solution (Joulie's solution) due to nausea and vomiting.

Plain radiography shows a radiolucent band at distal phalanx of right thumb. (figure 1) Thoracic kyphosis with Cobb's angle of 52.4 degree from T2-L1 with wedge compression fracture of L2 vertebrae are also shown. (figure 2) MRI spine revealed Lumbar spondylosis and degenerative disc disease at L4-L5. Whole body bone scan shows active bone lesion at multiple ribs bilaterally, L1-L2 spine, both SI Joints, right femoral neck and both ankles. Bone marrow biopsy was done but unremarkable findings.

An OCTREOTIDE scan show result of no any tissue somatostatin receptor. Parathyroid (MIBI Pertechnetate) shows an enhancing nodule measuring about 0.5×1.1 cm locate at lower pole of

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right parathyroid gland. (figure 3) For further information of tumor location, MRI of neck and thorax revealed elongate broad based dural lesion in posterior aspect of spinal canal at T5-T6 level, measuring about 0.8×1.3×2 cm in AP, transverse and vertical dimensions, respectively. (figure 4)

We performed standard midline approach and underwent T5 - T6 laminectomy without instrumentation. All the bony structures are unremarkable. The tumor is very loosely attached to the dura. (figure 5) It can be removed totally. Postoperatively, the patient's neurological examinations remained intact.

By the 6th day after tumor removal, serum phosphate level reached the normal range (2.5 mg/dl). (figure 5) Histological of the specimen shows spindle cell neoplasm. Her symptoms were completely improved. And at 6-month follow-up, she was no recurrence of TIO.

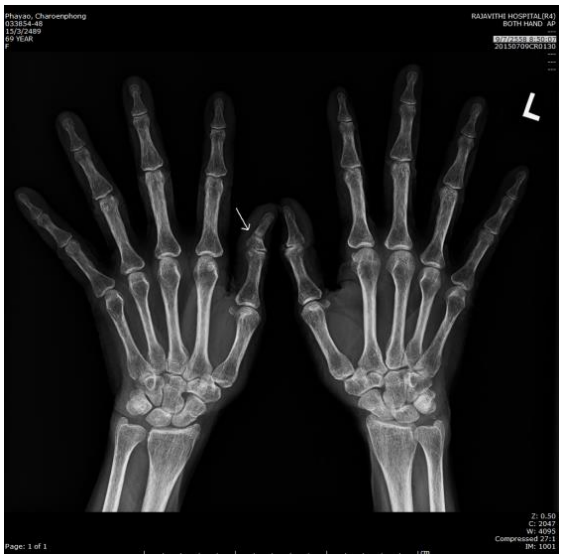

Fig. 1 A transverse line of pseudofracture of the distal phalanx of her right thumb. Juxta-articular osteopenia around metacarpo-carpal and metacarpo-phalangeal joints. (white arrow)

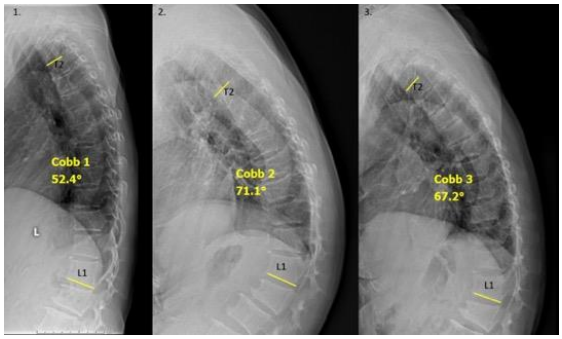

Fig. 2 A plain X-ray films of thoracic spine in lateral view taken at 2 years, 1 year prior to the surgery and after the surgery respectively.

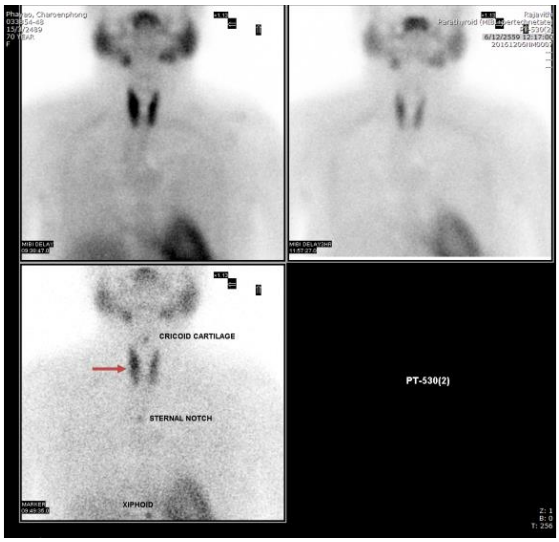

Fig. 3 Parathyroid (MIBI Pertechnetate) shows an enhancing nodule measuring about 0.5×1.1 cm locate at lower pole of right parathyroid gland. (red arrow)

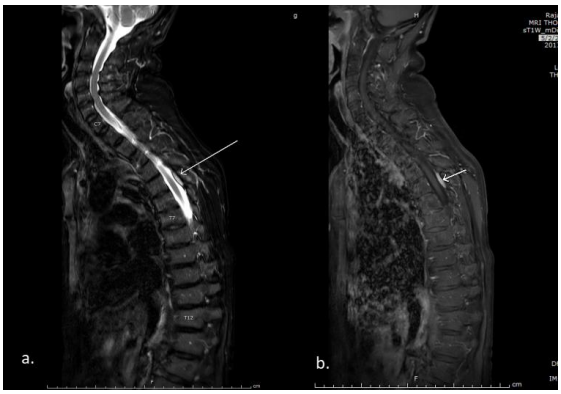

Fig. 4 MRI of neck and thorax revealed elongate broad based dural lesion of isosignal in T1W, hypersignal in T2W (a.) and T1W fat suppression with Gadolinium contrast enhancement (b.) in posterior aspect of spinal canal at T5-T6 level (white arrow), measuring about 0.8×1.3×2 cm in AP, transverse and vertical dimensions, respectively. There was no evidence of adjacent spinal cord or nerve root compression.

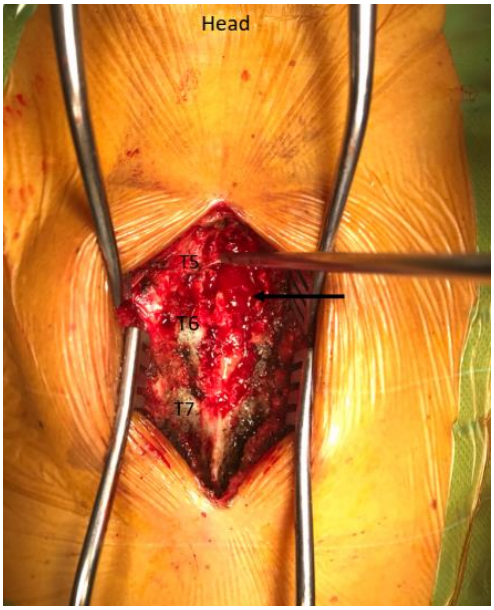

Fig. 5 The dark red epidural tumor size 1.7×1.5×0.6 cm adjacent T5-T6 laminar. (black arrow)

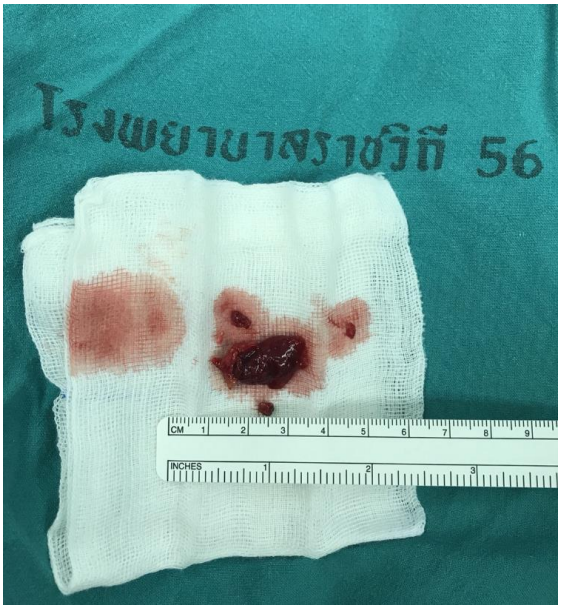

Fig. 6 Tumor size is 1.7×1.5×0.6 cm.

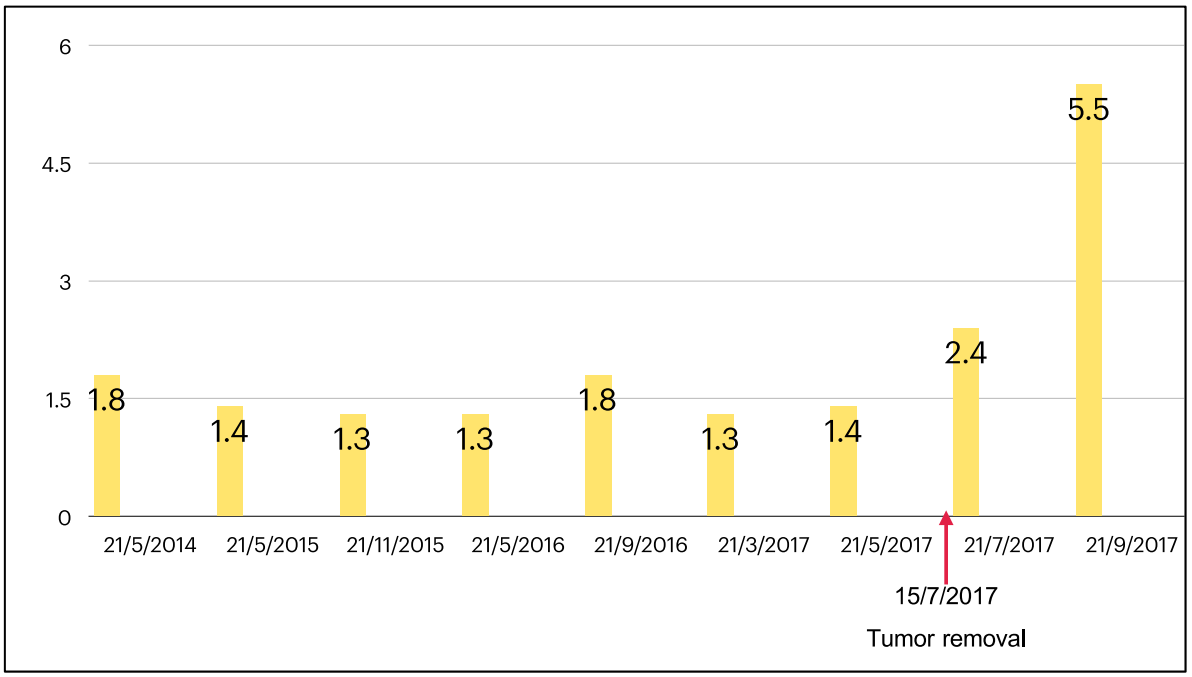

Fig. 7 Level of phosphorus in each visit. Her phosphorus level has been low since her first visit after her tumor removal surgery was done on July 15th, 2017. By the 6th days later, her phosphorus level reached its normal level. (Normal range 2.5-4.5 mg/dl)

Discussion

Clinical features of TIO consist of body pain, muscle weakness, bone fractures, hypophosphatemia from urine phosphate wasting and high level of circulating FGF-23. There is still no reported epidemiology of TIO. From most of TIO reports[1-6] show it occur in patient with age around 45 years old. There is no race and gender difference in epidemiology.

As stated before, TIO is rare. Its presented symptoms are very broad and very generic. TIO is mostly unaware of and unrecognized to be included in differential diagnosis. There is a report of delayed diagnosis of TIO which took 12 years before TIO was diagnosed and treated[4].

Pathophysiology of this condition begins with FGF-23 secreted by the tumor, FGF-23 will suppresses renal phosphorus resorption. Lowering serum phosphorus level decreases the amount of activation of vitamin D. Decreasing activated vitamin D directly affects bone mineralization which cause rickets in children or osteomalacia in adults.

TIO can be diagnosed by its common symptoms (body pain, muscle weakness and bone fractures) with hypophosphatemia. To study severity of urine phosphate wasting, tubular renal absorption of phosphate (TRP) is an accurate method to access. Calculation of TRP requires measuring concentrations of plasma and urine phosphate (P_p and U_p) and creatinine (P_{cr} and U_{cr}) in specimens and then calculate via this equation[6];

$$TRP = 1 - \{(U_p/P_p)\times(P_{cr}/U_{cr})\}$$

Normal TRP is 85% - 95% which will be decreased in TIO patients. To achieve accurate measurement, the patient should not be on any phosphorus supplement and blood and urine sample should be collected around the same period. Other helpful investigations include parathyroid hormone, serum vitamin D, serum calcium, alkaline phosphatase and FGF-23 level. According to TIO these findings should be high alkaline phosphates with normal serum calcium and normal or slightly subnormal vitamin D level. Parathyroid hormone usually maintains its normal level yet in some cases with prolonged low level of vitamin D, high level of parathyroid hormone can be presented from patient body reaction as secondary hyperparathyroidism.

TIO in very old patients might be misdiagnosed with postmenopausal osteoporosis. From the series of 144 TIO cases of Yan Jiang[5] in 2017 showed 37 cases of TIO misdiagnosed as osteoporosis. The patients, 100% presented with body pain, 86.5% with bone fractures, 25 of these 37 was undergone dual-energy X-ray absorptiometry (DXA) and treated with calcium supplement with vitamin D, calcitonin, or bisphosphonates.

The lesion of tumor can involve any soft tissue or bony site, although involvement of the extremities is more common than axial skeleton. The spine is extremely rare location of oncogenic osteomalacia and difficult to find.

As stated before, finding the anatomical location of FGF-23 producing tumor might be the most difficult part since they are often small, slow growing and can occur anywhere in the body. The total tumor removal will eradicate source of extra-secretion of FGF-23 completely and TIO will be cured. To locate the causative tumor, a stepwise approach is recommended[6].

1. Complete thorough physical examination especially palpable subcutaneous mass and tumor of nasal or oral cavity which are often ignored.

2. The functional imaging which can locate the causative tumor. Most of phosphaturic tumor express somatostatin receptor and somatostatin receptor (SSTR) scintigraphy has been proposed as a valuable option in imaging TIO associated tumors. The often-used method is Octreoscan™ which can be used as an adjunction to SPECT scan or CT scan. Octreoscan is successfully used to locate tumors in up to 95%[5].

After rough location of tumor is found by functional imaging, detailed imaging techniques such as CT or MRI should be followed especially for surgery planning.

If located tumor is more than one location, FGF-23 venous sampling by inserting venous catheter under fluoroscope to the vein corresponding to the tumor bed, compare the concentration of each sites to determine which is the culprit. FGF-23 venous sampling has a specificity of 71% and sensitivity of 87%[7].

Complete tumor resection with free margin is the definite curative treatment for TIO.

Minisola[8] reported using postoperative radiation in positive margin resection but its data is limited. Phosphorus and FGF-23 level generally will go up to their normal level in 5 days after the operation. Occasionally, culprit tumors may be difficult to address, or found the exact location yet open surgery would likely introduce significant morbidity. Image-guided radiofrequency ablation is an alternative treatment. There are very few reports indicating the achievement of long and complete remission in patients with TIO in whom the positive margins of the resected tumor were treated with radiotherapy. However, tumor removal surgery remains the treatment of choice.

If tumor cannot be located at all or complete resection is not possible, Pablo[6] suggested a guideline for medical treatment for TIO including administration of phosphorus supplement as the mainstay of treatment. Primary goal of the treatment is to reach at lower end of normal range of age-appropriate level of phosphorus. This will improve the bone disease shown by bone biopsy.

Phosphorus supplements should be administrated at least 3-4 times per day. Calcitriol/alfacalcidiol for prevent progression of osteomalacia via regulate the level of both phosphorus and serum parathyroid hormone. Chronic treatment with vitamin D may lead to hypercalciuria and renal stones, periodic work-up for urine calcium should be performed. The treatment regimen is to give 15-60 mg/kg per day of phosphorus divided into 4-6 doses. Calcitriol/alfacalcidiol is given at 15-60 ng/kg per day.

Development of medical treatment of TIO with unrespectable tumors using FGF-23 monoclonal antibody or KRN23 which aims to decrease the activity of FGF-23. KRN23 appears to

safely increase renal phosphate reabsorption, serum phosphate and 1,25(OH)2D in patients with X-linked hypophosphatemic rickets. Now this report KRN23 reaches its phase III of clinical trials[11].

In our perspectives compared to most reports on TIO, this patient first presented with typical clinical features of TIO which included body pain, bony fractures and other consequential osseous deformities. Her laboratory shows normal serum calcium level, hypophosphatemia, abnormally high alkaline phosphatase and high FGF-23. An OCTREOTIDE Scan which show result of no any tissue somatostatin receptor. We have found the culprit tumor's location by MRI Neck and Thorax. By the 6th day after tumor removal, serum phosphorus level reached normal range. Patient's symptoms were improved without phosphorus supplements. Histological reports show its cell type as spindle cell tumor.

Table 1 Comparing our case with previous TIO studies.

Author	Sex, Age	Affected level	Signs & Symptoms	Radiography	Laboratory Results	Given Treatments	Histological findings	Clinical Outcomes
Stone, 1992	Female, 33	T3-4	Low back pain, Weakness of legs	Compression T3-4	Hypophosphatemia	Surgery, Radiotherapy, Supplementary Vitamin D, Phosphate and Calcium	Neuroendocrine Tumor	Good
Nielsen, 2001	Male, 14	Sacrum	Bone pain, Skeletal abnormalities	N/A	Hypophosphatemia, Hypocalcemia, Low Vitamin D, High alkaline phosphatase	Chemotherapy	Osteosarcoma	N/A
Folpe, 2004	Female, 32	C1	N/A	N/A	N/A	Surgery, Radiotherapy	Malignant PMTMCT	Recurrence
Elena et al., 2009	Male, 57	T4	Paresthesia, hyperreflexia, Multiple bone fracture	T4 destruction	Hypophosphatemia, low vitamin D, high alkaline phosphatase	Surgery, Supplementary Vitamin D and Phosphate	PMT	Good
Our case	Female, 71	T6	Bone pain, bone fracture, kyphosis, weakness	Thoracic kyphosis	Hypophosphatemia, high alkaline phosphatase	Surgery, Supplementary Vitamin D and Phosphate	Spindle cell Tumor	Good

Conclusion

TIO is a paraneoplastic syndrome caused by small FGF-23 secreting tumor which can occur in any part of the body. Locating the tumor by thorough physical examination and functional imaging and complete tumor resection can in completely cure this condition. If tumor cannot be located or tumor is in the dangerous place which can introduce morbidity, medical treatment can sufficiently control the severity of TIO.

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เนื้องอกกระตุ้นการเกิดโรคกระดูกอ่อนในผู้ใหญ่ (Tumor induced osteomalacia)

เฉลิมพล กินรี, พบ, ธนิตา ปัญญาอมรวัฒน์, พบ, อธิคม เมธาเธียร, พบ, ยงยศ เหลืองวิชชเจริญ, พบ

ผู้ป่วยหญิงไทย อายุ 71 ปี มาโรงพยาบาลด้วยอาการ อ่อนแรง ปวดเมื่อยตามร่างกาย เป็นเวลา 2 ปี ตรวจร่างกายไม่พบความผิดปกติ ผลเลือดพบค่าฟอสเฟตในเลือดต่ำ และค่า alkaline phosphatase สูง ภาพถ่ายทางรังสีพบรอยหักของกระดูกนิ้วหัวแม่มือขวาโดยที่ไม่มีประวัติอุบัติเหตุ และพบกระดูกสันหลังระดับอกค่อมลง การตรวจต่อมพาราไทรอยด์สแกนพบจุดที่ด้านขวาล่าง และตรวจคลื่นแม่เหล็กไฟฟ้าบริเวณคอและอก พบเนื้องอกบริเวณ epidural ของกระดูกสันหลังระดับอกข้อที่6 ผู้ป่วยได้รับการรักษาด้วยการผ่าตัด ภายหลังการผ่าตัด 6 วัน พบว่าค่าฟอสเฟตในเลือดกลับมาปกติ และอาการของผู้ป่วยขึ้น ผลตรวจชิ้นเนื้อพบเป็น spindle cell tumor

คณะผู้วิจัยได้แสดงถึงการค้นหาสาเหตุของ Tumor induced osteomalacia ซึ่งทำได้ยาก ต้องอาศัยการตรวจร่างกายและการตรวจพิเศษเพื่อค้นหาตำแหน่งของเนื้องอก และการรักษาด้วยการผ่าตัดทำให้ผู้ป่วยหาย มีผลเลือดกลับมาปกติ