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Case report

A case report of mesenchymal scapular FGF secreting tumor: Importance of follow up in tumor induced osteomalacia

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ABSTRACT

A 46-year-old Asian male with history of atraumatic fracture of femur (requiring the use of a walker), muscle cramps and loosening teeth presents to Endocrine clinic. He had elevated parathyroid hormone, severely low phosphorus, elevated bone-specific ALP, with normal serum and urine calcium. He was found to have elevated FGF 23 levels, but initial functional and anatomic imaging was negative for any localizing tumor. With persistent follow-up and serial imaging, after 3 years, a 2.2 cm right scapular mass was found on MRI. Since it was also visualized on PET/CT, this was suspected to be the cause of his severe hypophosphatemia. He underwent surgical excision and pathology revealed a phosphaturic mesenchymal tumor after excision. Tumor induced osteomalacia is a rare, acquired paraneoplastic syndrome in which a tumor that secretes FGF23 leads to decreased renal phosphate reabsorption, resulting in hypophosphatemia, and bone demineralization. Diagnosis is challenging as common presenting symptoms are nonspecific, but when followed up closely with proper diagnostic modalities, identification & removal of the culprit lesion is usually curative.

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Introduction

Tumor induced osteomalacia (TIO), also known as oncogenic osteomalacia, is a rare, acquired paraneoplastic syndrome in which a tumor (usually benign and mesenchymal in nature) produces fibroblast growth factor 23 (FGF23) and/or other proteins that lead to decreased renal phosphate reabsorption.

This ultimately results in hypophosphatemia, low 1,25OH vitamin D and bone demineralization [1]. Diagnosis is challenging as common presenting symptoms are nonspecific, and they may comprise of fatigue, bone pain, and musculoskeletal weakness, however; TIO also frequently presents with insufficiency fractures, which should raise suspicion of a pathologic process. The hallmark laboratory finding is hypophosphatemia, often with an elevated FGF23 level in the blood [1].

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It is important to localize the culprit tumor, as complete surgical excision is curative and the biochemical abnormalities typically begin to improve 3 months after surgery [2]. Diagnostic modalities for tumor localization include whole body PET/CT, MRI, and scintigraphy using radiolabeled octreotide; although, even with extensive imaging, in up to 35% of presumed TIO cases, the primary tumor is not identified [3].

Case presentation

A 46-year-old Asian male was referred to the Endocrine clinic after sustaining a subacute fracture of the left femoral diaphysis, for which he underwent surgery. Prior to the surgery, his symptoms were atraumatic left thigh pain, muscle cramps and loosening of the lower teeth requiring implants. Physical examination was notable for him using a walker, but no bony abnormalities were palpated or visualized. During the initial encounter, complete blood count and renal function were normal. Notably, PTH level was elevated (84.3 pg/mL) and phosphorus was low (1.8 mg/dL). 25-hydroxy vitamin D was mildly decreased (25 mg/dl). Alkaline phosphatase (ALP) & ALT were elevated (160 U/L & 56 U/L respectively), but ALT was normal. Bone-specific ALP was elevated (74.8 mcg/L). Urine phosphate to creatinine ratio was elevated to 0.168, inappropriate for severe hypophosphatemia. Both serum calcium & urine calcium excretion were normal. Thyroid function was within normal range.

Differential diagnosis, investigations, and treatment

During the initial presentation, labs were concerning for normocalcemic primary hyperparathyroidism given elevated PTH, decreased phosphorus and an insufficiency fracture (Fig. 1). To rule out secondary hyperparathyroidism, patient was started on Ergocalciferol 50,000 IU weekly. When PTH normalized but phosphorous remained severely low, hyperparathyroidism was ruled out as the etiology for hypophosphatemia.

Due to elevated ALP and bone-specific ALP, Paget's disease was considered another possibility. However, his radiology imaging and other parts of his clinical course was not consistent with Paget's (ie, hypophosphatemia and atraumatic fracture)

Because of persistent severe hypophosphatemia without hyperparathyroidism as a cause, serum FGF23 was obtained to rule out oncogenic osteomalacia. During his workup, he was started on NeutraPhos supplementation as well as calcitriol to try and improve his labs and symptoms. FGF23 was significantly elevated (246 RU/mL; normal <180 RU/mL), therefore his overall picture was concerning for an unidentified tumor producing FGF23 leading to his osteomalacia, insufficiency fractures and hypophosphatemia. PET/CT and Octreotide scans were performed, both negative for a localizing tumor. Patient continued to closely follow-up with endocrine and despite progressively increasing FGF23 levels (423 RU/mL),



Fig. 1 – X ray of left femur showing nondisplaced oblique proximal left femur involving the medial cortex.

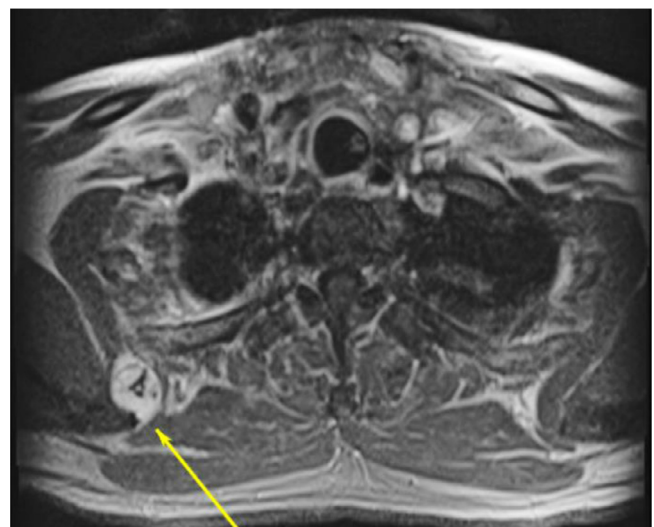


Fig. 2 – T1 MRI upper thorax axial view showing a round low T1 intensity inter-muscular right superior posterior chest wall mass with central calcification (yellow arrow). (Color version of Figure is available online.)

there was still no discrete tumor on exam nor imaging for 2 years; repeat PET/CT was negative. However, repeat Octreotide scan (Fig. 2) showed new areas of uptake in skull base, nose, supraclavicular region, hila of lungs and liver compared to prior scans, thus prompting MRI head and neck (Figs. 3 and 4) which finally demonstrated a 21.5 × 16.9 × 22.8 mm round inter-muscular right superior posterior chest wall mass with

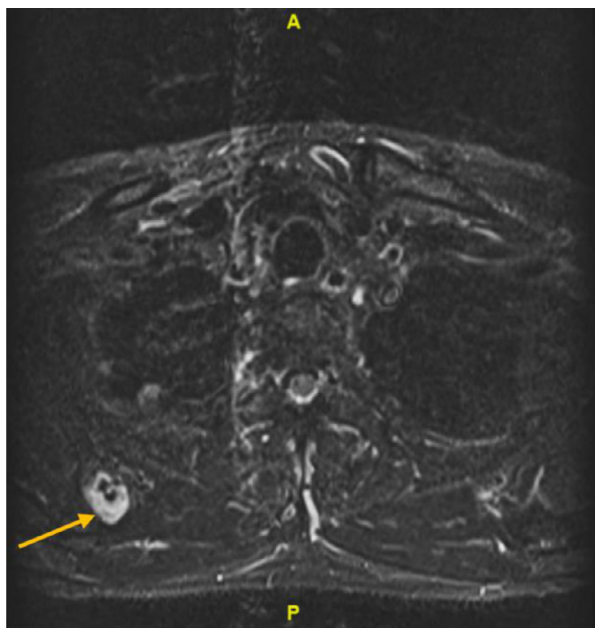


Fig. 3 – MRI upper thorax axial view with increased STIR (Short TI Inversion Recovery) signal intensity with peripheral contrast enhancement in the right posterior chest wall.

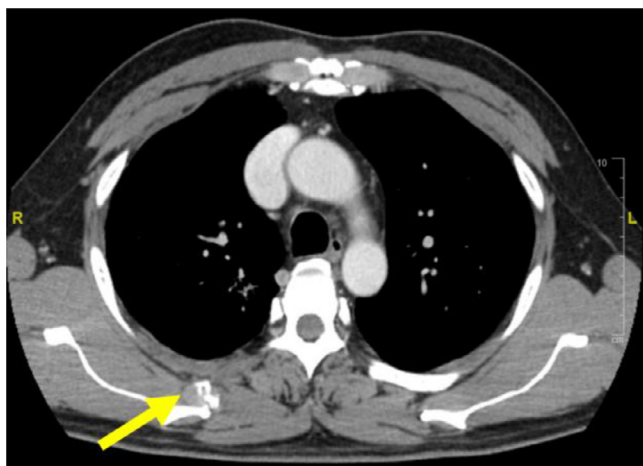


Fig. 4 – CT chest axial view showing soft tissue lesion with internal calcification deep to the medial border of right scapula (yellow arrow).

central calcification adjacent to deep medial right scapula posterior to serratus anterior, medial to subscularis and anterolateral to rhomboid major muscle with low T1 and high STIR signal intensity with peripheral contrast enhancement, concerning for mesenchymal tumor. Patient was referred to surgical oncology and after case discussion in an interdisciplinary tumor board conference, it was recommended that the patient undergo CT chest and follow up with medical and surgical oncology. After confirming findings in CT (Fig. 5), patient underwent excision of the right scapular tumor with histopathology confirming it as a phosphaturic mesenchymal

tumor. The resection margins were negative for tumor and 3 benign lymph nodes were seen.

Outcome and follow-up

Patient followed up with endocrinology, medical oncology, and surgical oncology after the surgery and reported feeling much better apart from some postsurgical stiffness, with resolution of his cramps and muscle weakness. FGF 23 level was checked 3 weeks after the surgery and was markedly improved (415 RU/mL preop to 37 RU/mL 4 days postop). Phosphorus level normalized 4 days after surgery, which was notably not optimized even with 2 years of significant phosphate and calcitriol supplementation (Fig. 6)

Discussion

TIO is an acquired form of vitamin D-resistant osteomalacia that typically presents with bone pain, muscle weakness & fractures, however it can manifest with atypical features [5,6]. It is important to recognize the pattern of biochemical derangements that includes hypophosphatemia with phosphaturia, low to normal calcium, low to inappropriately normal $1,25(\text{OH})_2$ vitamin D and an elevated FGF-23 [6,7]. Other similar conditions that are important to consider, especially in the younger age spectrum, are autosomal dominant hypophosphatemia and X-linked hypophosphatemia, where genetic mutations occur in FGF23 & PHEX genes respectively. Therefore, it is important to check for these mutations when in doubt [8,9].

Diagnosing TIO can be particularly difficult when the responsible tumor cannot be localized, which occurs frequently in this syndrome. A meticulous physical examination is very important to look for subcutaneous soft tissue tumors that might have been ignored or not detected [10]. However, most patients do ultimately require special imaging by means of Octreotide scan or PET/CT, and if an area of lesion is suspected, it can be further worked up with dedicated MRI, CT or ultrasound [7]. In addition to the above, ^{68}Ga -DOTATATE has been demonstrated to have good sensitivity and specificity in independently localizing the phosphaturic mesenchymal tumors [11,12]. Even if the tumor is not localized, it is important to continue closely following these patients with serial physical examinations, serial FGF levels, biochemical profile and necessary imaging, as these tumors may slowly grow with their revelation, as it did with our patient, who was found to have the scapular mass after 3 years of symptom onset.

In 2004, Folpe et. al published the histologic characteristics of TIO in 32 cases. The cases ranged from primary mesenchymal tumors comprising about half of the cases, with the remaining being a hemangiopericytoma, osteosarcoma, or giant cell tumor. Common histological findings were hypocellularity, myxoid change, calcified matrix, and bland spindled cells. Ninety percent of the tissues stained positive for FGF-23 by immunohistochemistry or RT-PCR [13]. In our patient, histopathology demonstrated “calcified cartilage-like ar-

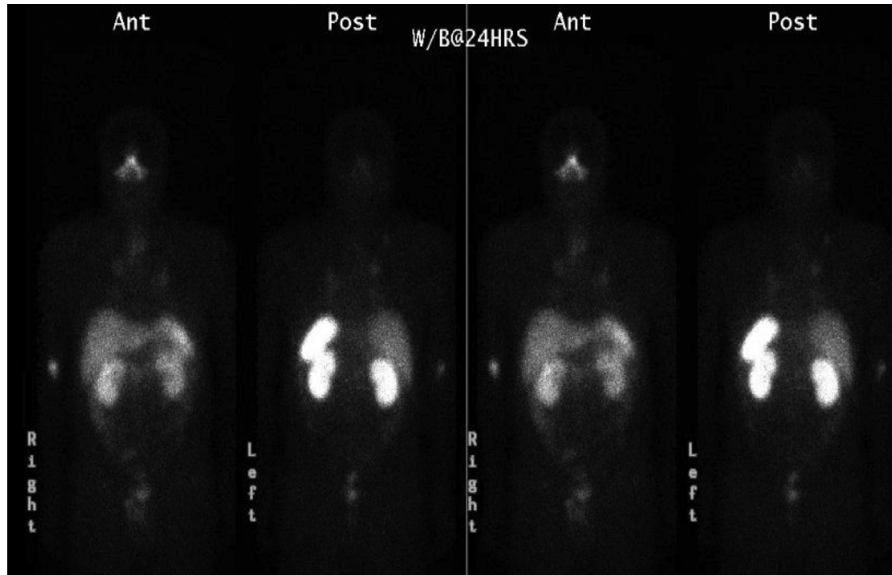


Fig. 5 – Increased radiotracer uptake noted in the nasopharynx, left supraclavicular region, superior mediastinum, bilateral hila and at right antero-inferior aspect of the liver.

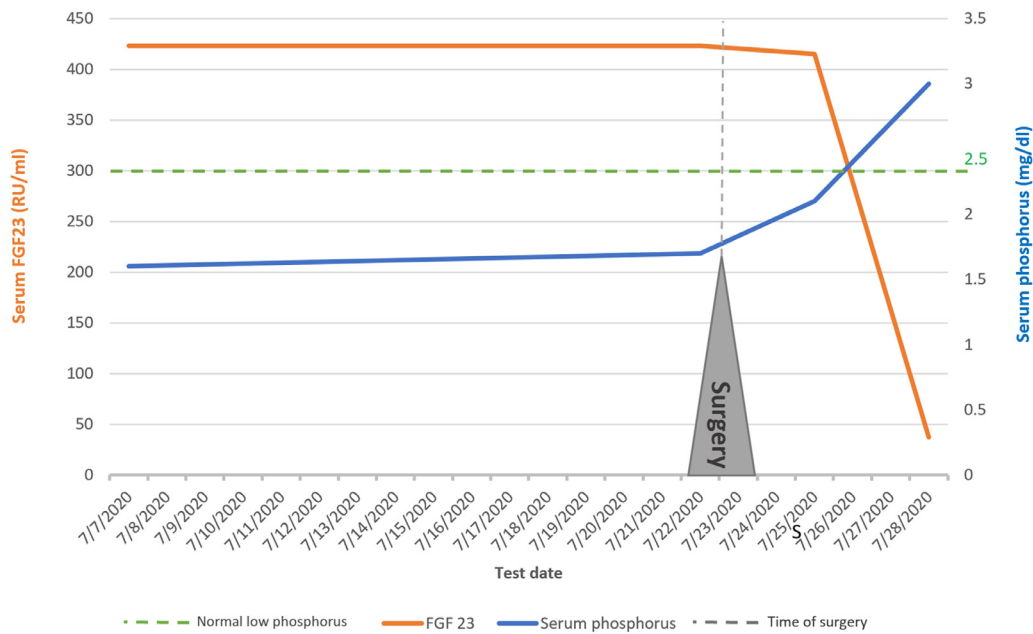


Fig. 6 – Graph showing trends of FGF 23 and serum phosphorus before and after surgery (gray line). FGF 23, fibroblast growth factor 23.

eas, uniform, noncalcified epithelioid cells, and scattered osteoclastic giant cells.” There was possible bone involvement of the tumor and immunohistochemistry was positive for podoplanin and vimentin, with focal positivity for S100 protein and negative for CD68 and keratins AE1/AE3. IHC or RT-PCR was not done on our patient’s resected tumor.

Secondary TIO can occur with epidermal nevus syndrome, prostate cancer, fibrous dysplasia of bone, or neurofibromatosis, in which case the treatment should be directed towards treating the primary condition [14,15,16,17].

Surgical resection of the culprit tumor is the most definitive treatment. Serum phosphorus levels increase back to normal within 1-2 weeks after surgery and the musculoskeletal pain usually resolves within 3-6 months [18,19]. In our patient, we observed complete correction of serum phosphorus within 3 weeks after surgery, although it was not checked in between. His muscle pain and weakness had partially resolved within 4 weeks.

Patients with TIO usually have an excellent prognosis with resolution of the disease after complete surgical resection, al-

though, there have been instances of recurrence [18]. In the case of incomplete resection of tumor, Burosumab – a monoclonal antibody against FGF23, can be used, which is FDA-approved for TIO and has shown to normalize serum phosphorus levels, improve bone mineralization, decrease pain & allow for better physical functioning as per an ongoing open-label Phase 2 study, however its cost might be a limiting factor for many patients [4,20]. Postsurgical surveillance should be conducted with periodic monitoring of serum FGF-23 and biochemical markers to ensure remission.

Conclusion

TIOs are usually occult and when suspected need a close eye during follow up as tumors may take years to declare themselves. They can be located anywhere from the feet to the skull so comprehensive imaging is required. Even though these tumors can be small and unassuming; surgery can be curative and the improvement in hypophosphatemia and symptoms rapid and profound.

Patient consent

Patient consent has been obtained.

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