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BMH Med. J. 2019;6(4):140-144. **Case Report**

A Tiny Tumour That Broke His Hip: A Rare Case Of Tumour Induced Osteomalacia In A Patient With Treacher Collins Syndrome

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Abstract

Tumour induced osteomalacia is a rare paraneoplastic syndrome, resulting in renal phosphate wasting. Patient presents with nonspecific symptoms and is often misdiagnosed. This case illustrates the difficulties encountered in the diagnosis of tumour induced osteomalacia in a patient with Treacher Collins syndrome and in identifying the responsible tumour.

Keywords: Tumour induced Osteomalacia, Phosphaturic Mesenchymal tumour

Introduction

Tumour induced osteomalacia (TIO) is a rare paraneoplastic syndrome associated with renal phosphate wasting. Tumour cells produce Fibroblast growth factor 23 (FGF-23), a physiological regulator of serum phosphate level. Overexpression of FGF-23 leads to increased clearance of phosphate in urine, mobilization of calcium and phosphate from bone, and the reduction of osteoblastic activity causing osteomalacia [1].

The patient usually presents with gradual muscle weakness, fatigue, bone pain, pathological fractures, walking difficulty, proximal muscle atrophy, and osteopenia. Patients have hypophosphatemia, hyperphosphaturia, elevated levels of alkaline phosphatase (ALP), normal to low serum vitamin D and normal levels of calcium and parathyroid hormone (PTH). Sometimes the causative tumour is easily visible or palpable, but often the tumours are small and difficult to detect. The correct diagnosis is often delayed and misdiagnosed as having prolapsed intervertebral disc, spondyloarthritis, osteoporosis or hyperparathyroidism [2].

After diagnosis treatment is delayed due to difficulties in locating the primary causative tumour, as these tumours are often small, slow growing, and can occur anywhere in bone or soft tissue. [3] Complete excision is curative and all the symptoms resolve following excision of the primary tumour.

Case History

(Fig-1 Features of Treacher collins syndrome:- down slanting bilateral palpebral fissure, Hypoplastic supra-orbital and zygoma, hypoplastic maxilla and mandible and Microtia.)

This middle aged person with Treacher Collins syndrome presented to orthopaedician with repeated attacks of musculoskeletal pain, generalised fatigue, bone pain over arm, leg and back, and was being managed in with analgesics and other supportive measures. Features of Treacher Collins syndrome noted in him were down slanting bilateral palpebral fissures, hypoplastic supra-orbital and zygoma, hypoplastic maxilla and mandible and microtia.

These episodes worsened with increasing frequency and he became wheelchair bound in 2 years. Suspecting spinal nerve pathology patient underwent MRI which was inconclusive. He had normal calcium and low phosphate levels, thus suspecting osteomalacia he was started on calcium and Vitamin D supplements. His symptoms did not improve and he was referred to endocrinologist for evaluation of metabolic bone disease.

The patient had a normal serum concentration of sodium, potassium, calcium, magnesium, parathyroid hormone, elevated ALP. On further evaluation, his hypophosphatemia and high 24 hours urinary excretion of phosphate, suggested renal phosphate wasting. Considering the patient's age, negative family history for bone and mineral disorders, a diagnosis of TIO was considered. Serum FGF-23 level was evaluated which was found elevated. Patient underwent whole-body Gallium 68 DOTA-NOC PET/CT scan and the tumour was located in posterior alveolus of left maxilla. The causative tumour was resected and local flap used to cover the defect.

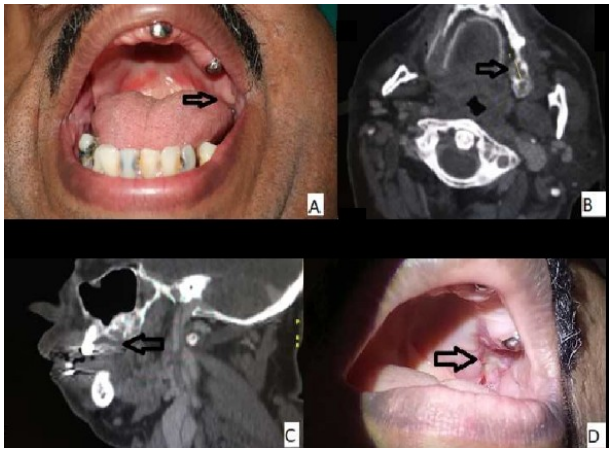

Figure 1: A and D showing tumour location preoperative and post operatively respectively. C and D are CT images (arrows denoting tumour location).

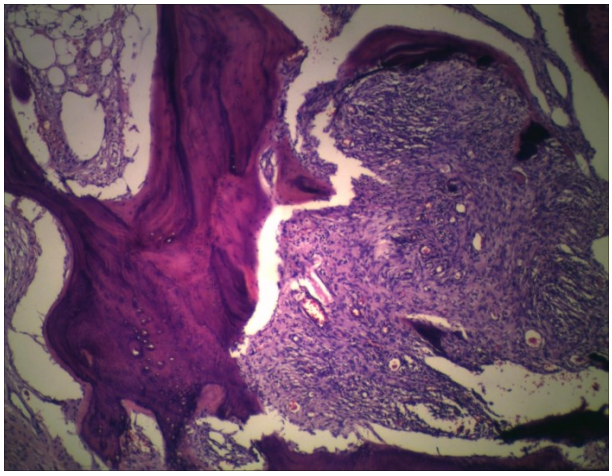

Figure 2: Histopathological image depicting ossification (Arow marked)

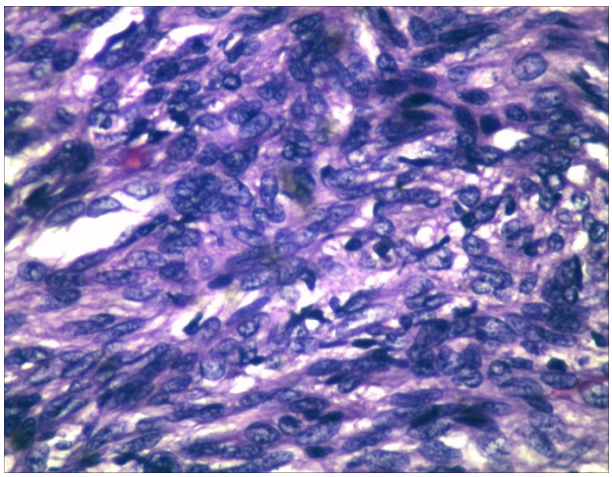

Figure 3: High power histopathological image showing Spindle cells in interlacing fascicles.

The histopathological report suggest spindle cell neoplasm with foci of ossification and irregular grungy classification. The spindle cells were positive for smooth muscle actin and CD34 and negative for desmin. Postoperatively patient showed dramatic improvement in his symptoms. His serum phosphate values increased, serum FGF-23 and urinary phosphate values decreased and reached normal value in one month.

Discussion

TIO is also known as oncogenic hypophosphatemic osteomalacia is a rare paraneoplastic syndrome. It is most often associated with small benign tumours of mesenchymal origin (80%) known as Phosphaturic Mesenchymal Tumour (PMT). It is also associated with hemangiopericytoma, giant cell tumour of bone, and osteosarcoma. It was first published in 1947 by McCance. In 1959 Prader described the association between tumour and osteomalacia and in 1987 Weidner and Cruz coined the term PMT. Between 1970 and 2013, 404 articles containing PMT cases have been published in the literature. But, due to presentation with nonspecific symptoms and absence of serum phosphate level in routine blood chemical studies there is often a long delay between the appearance of symptoms and diagnosis with definitive treatment ranging from 1.5-28 years, the average being 6.7 years [4].

PMT are rare tumours most often seen in middle-aged persons without any gender predilection occurring throughout the body, 56% in lower extremities, 5% in the upper extremities, 3% in the hip, 31% in the head and neck, and 5% in thorax region. [5] The tumours secrete FGF-23, a peptide hormone of phosphate metabolism, physiologically produced by osteocytes and osteoblasts. FGF-23 inhibits sodium-phosphate co-transporters in the proximal tubular cells of the kidney, impairing reabsorption of phosphates in proximal tubules. It also downregulates production of 1-α hydroxylase enzyme, thereby decreasing conversion of 1-hydroxyl Vitamin D to 1,25-dihydroxy Vitamin D. There is renal excretion of phosphate and less absorption from gut leading to hypophosphatemia but the calcium metabolism remains unaffected [3].

Clinical diagnosis of renal phosphate wasting with increased serum FGF-23 diagnostic of TIO. Once diagnosed primary tumour can be identified via octreotide scintigraphy or Gallium 68 DOTA-NOC PET/CT scans [6,7]. Delay in diagnosis imparts considerable morbidity. If tumour can't be located, patient should be given oral supplementation of active vitamin D metabolites. It increases the intestinal absorption of phosphate and suppresses PTH production. Patients should also be closely monitored for complications, as long-standing hypophosphatemia can lead to progression of osteomalacia and pathological fractures. Severe hypophosphatemia can lead to ATP depletion, and affect the cardiopulmonary system by impairing myocardial and diaphragmatic contractility. It can also affect the hematopoietic system leading to hemolysis and leukocyte dysfunction [8].

Complete and definitive surgical resection is the treatment for TIO. Octreotide replacement therapy has also been shown to be useful for octreotide-positive patients. Phase-1 clinical trials of anti-FGF-23 antibodies for the treatment of X-linked hypophosphatemic rickets shows promising results and may be applicable for TIO patients in the future [9].

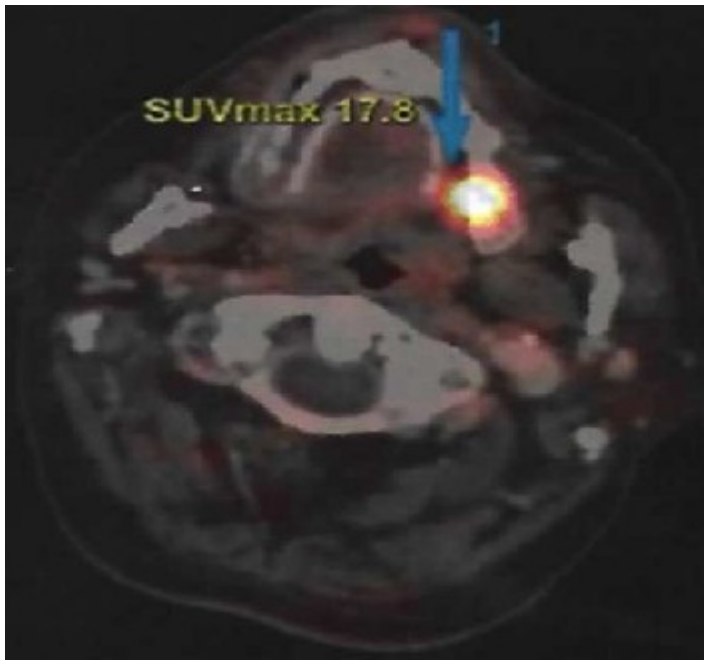

Figure 5: The tumour as identified by Ga-68 DOTANOC scan)

Conclusion

Tumour-induced osteomalacia should be considered in the differential diagnosis of all patients with musculoskeletal symptoms associated with hypophosphatemia. Hypophosphatemia in the absence of family history, rapidly progressing recent onset of symptoms in an adult suggests TIO. Awareness of this acquired metabolic abnormality and early recognition of the condition remains of the utmost importance. In this case a small tumour was present in an hypoplastic incompletely developed maxilla. Our case shows a rare combination of a developmental disorder as Treacher Collins syndrome associated with a PMT.

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