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No significant differences in macroscopic and histological appearance between single and triple intra-articular injection of mesenchymal stem cells for repair of cartilage defect in a canine model

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ABSTRACT

Significant hypophosphatemia in adult is uncommon, in which the most common culprit being Vitamin D deficiency. Hypophosphatemia in adults, require proper attention as it may indicate paraneoplastic effect of mesenchymal tumour (Fibroblast growth factor 23 secreting tumour). The diagnosis of such condition at early stage, along with prompt treatment can correct hypophosphatemia and improve the patient symptomatically. Here we are presenting a case of 48 years old female who had severe hypophosphatemia and on work up found to have FGF23 secreting mesenchymal tumour of the naso-ethmoid bone, surgical removal of which corrected hypophosphatemia and showed clinical improvement.

1. INTRODUCTION

Osteomalacia is characterized by impaired mineralization of bone. TIO is an acquired form of osteomalacia which is characterized by severe hypophosphatemia leading to osteomalacia due to excess secretion of FGF23. Here we describe a case of 48 years old female who presented with chronic low backache and spontaneous fracture of bilateral femoral necks. Laboratory evaluation showed low phosphorus, low normal calcium, normal serum parathyroid hormone and 25-OH vitamin D, but significantly high FGF23. PET-CT showed bilateral multiple ribs sternal body, right sacral ala, bilateral inferior pubic rami and bilateral femoral neck fractures, along with a hypermetabolic heterogeneously enhancing, right naso-ethmoid mass. Functional sinus endoscopy guided biopsy of the naso-ethmoidal mass led to the diagnosis of a hemangiopericytoma. Forty-eight hours after surgical excision of the tumour, there was normalization of serum FGF23 and a rise in the serum phosphate level. The differential diagnosis of TIO needs to be considered in every adult patient with severe unremitting hypophosphatemia. A high index of suspicion can potentially reverse the underlying disease process and reduce further morbidity.

2. CASE REPORT

A 48 years old female with no previous comorbidities, presented to our institute with complaints of chronic low backache for 4-5 years, bony pain, difficulty in walking which progressively worsened to such an extent that she was bedridden at the time of presentation. She had been seen by orthopaedics and rheumatology earlier and was labelled to have osteoporosis. She was treated with calcium, vitamin D, pain killers (including NSAIDs), and also steroids to relieve her pain. DEXA scan done showed a T score of -2.7 suggestive of severe osteoporosis. There was no muscle weakness, wasting and paraesthesia. There was no history of fever, night sweats and weight loss. There was no obvious history of nephrolithiasis or symptomatic fractures. Her physical examination was unremarkable except for pain during movement of joints without any joint deformity. Review of her biochemistry revealed persistent hypophosphatemia, with levels ranging from 2 to 2.4 mg% (Normal: 2.5-4.9 mg%), along with elevated alkaline phosphatase in the range of 250 to 400 mU/ml (Normal: 46-116 mU/ ml). All other biochemical parameters including serum calcium, Vitamin-D, serum i-PTH, serum TSH, serum protein electrophoresis was normal. Trends of laboratory as below (Table 1).

Table 1. Trend of lab parameters over period of time

Laboratory parameters	2011	2012	2014	2015	7 days prior to surgery	48 hours post-surgery
Serum Creatinine (mg%)	0.87	NA	0.72	0.8	0.8	NA
Serum Calcium (mg%)	8.5	8.6	9.2	9.18	8.2	8
Serum Phosphorus (mg%)	NA	2	NA	2.41	1.2	2.1
Serum Alkaline Phosphatase (mU/ml)	421	257	414	202	278	124
Serum Vit-D (ng/ml)	NA	37	NA	37	160	NA
Serum i-PTH (pg/ml)	NA	NA	65.53	25	23.31	-

Her TmP/GFR was calculated 0.48 using nomogram of Walton and Bijvoet [1]. We reinvestigated her. Her laboratory values were as in Table 2.

Table 2. Lab parameters at time of admission

Laboratory parameters	Values
Serum Creatinine (mg%)	0.8
Serum Calcium (mg%)	8.5
Serum Albumin (mg%)	4
Serum Phosphorus (mg%)	1.2
Serum Alkaline Phosphatase (mU/ml)	278
Serum Vit-D (ng/ml)	160
Serum 1,25-OH Vitamin D (pg/ml)	38.6
Serum i-PTH (pg/ml)	23.31
Serum FGF 23 (RU/ml)	6170
24-hour Urinary Calcium (mg/24 hour)	86.6
Spot Urinary Creatinine (mg/dl)	68.5
Spot Urinary Phosphorus (mg/dl)	3.9

The result clearly demonstrated renal phosphate wasting. Having eliminated hyperparathyroidism and Fanconi's syndrome and with a high FGF23 value, we suspected TIO. A PET-CT was done which showed fractures in multiple ribs, sterna, body, right sacral ala, bilateral inferior pubic rami and bilateral femoral neck. A hyper metabolic, heterogeneously enhancing right naso-ethmoid mass was also detected (Figure 1).

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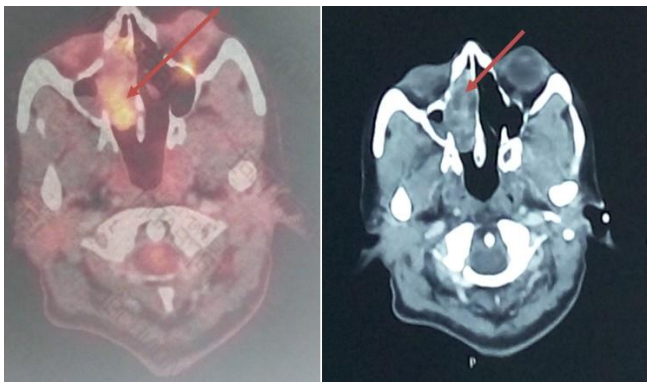

Figure 1. PET CT and CT showing hyper metabolic, heterogeneously enhancing right naso-ethmoid mass (as shown by red arrow)

FESS guided naso-ethmoidal biopsy was done which showed a hemangiopericytoma (with stag horn appearance of blood vessels) on histology (Figure 2).

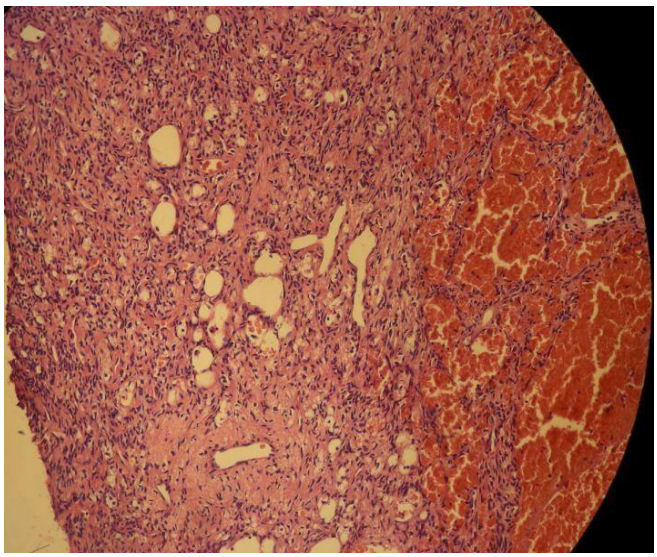

Figure 2. FESS guided naso-ethmoidal biopsy showing a hemangiopericytoma (with stag horn appearance of blood vessels)

Subsequently, Functional endoscopic sinus surgery guided full resection of the naso-ethmoidal mass was done. After 48 hours of surgery, her serum phosphorus increased to 2.1 mg%, serum alkaline phosphorus was decreased to 124 mU/ml, serum calcium 8 mg% and serum FGF23 decreased significantly to 34.7 RU/ml. After discharge she lost to follow up.

3. DISCUSSION

TIO is characterized by renal phosphate wasting leading to severe hypophosphatemia and its clinical manifestations. FGF23, a phosphatonin causes inhibition of sodium-phosphate co-transporters (NaPi-IIa and NaPi-IIc) localized in the proximal tubule leading to decreased absorption of phosphate and also inhibits vitamin D 1-alpha-hydroxylase thereby suppressing the production of 1,25-OH vitamin D [2]. In review article of 308 cases by Quoting Jiang, et al., about 46% were females and 56% were males with a mean age of 45.3 years, with 40% of tumours originate in bones and 55% in soft tissues. The most common location are the lower extremities (56%) followed by head (31%), and rarely it can be seen in the upper extremities (5%), thoracic region (5%) and hip (3%) [3]. Imaging modalities like PET-CT, octreotide

scintigraphy and Sestamibi parathyroid scintigraphy helps to locate occult tumour [3]. In our case the patient presented with bony pain and pathological fracture but there were no ENT complaints related with naso-ethmoidal mass which got detected incidentally during work up for TIO.

On the basis of histological finding of 16 cases of TIO, Weidner in 1991 named the tumours as phosphaturic mesenchymal tumours which were further subdivided into four categories [4]:

1) Mixed connective tissue variant (PMTMCT),
2) Osteoblastoma-like variant,
3) Non-ossifying fibroma-like variant, and
4) Ossifying fibroma-like variant.

Of four categories, the most common histologic variant was PMTMCT (70-80%) which consist of primitive stromal cells, prominent vessels, and osteoclast like giant cell. These are usually benign but rarely can be malignant [5]. Patients with TIO often present with nonspecific symptoms like generalized weakness, easy fatigability, bone pain, muscle weakness. Rarely can be presented with reduced height, and multiple spontaneous fractures, primarily in the ribs, vertebral bodies, and femoral neck. Because of above symptoms patients often visit multiple specialist like physician, rheumatologist, orthopedic surgeon and even physiotherapist. Biochemistry in TIO includes hypophosphatemia due to renal phosphate wasting, low levels of 1,25-di-hydroxy vitamin D due to inhibition of 1alpha hydroxylase and normal serum calcium and PTH. TMP/GFR was calculated with the help of nomogram of [1] from urinary and serum calcium, creatinine, and phosphorus levels. Definitive treatment of TIO is surgical excision of tumour so as to remove source of causative agent FGF23. After excision of tumour the serum phosphorus level normalizes by 5 days in most cases [6]. In our case as shown in Table 1, serum FGF23 level normalize after 48 hours of surgery and serum phosphorus became 2.1 mg%. In rare instance calcitriol or alfacalcidol or cinacalcet has been tried for the treatment of TIO patients which correct hypophosphatemia by inducing hypoparathyroidism [7]. Recently, phase I trial of injection of humanized anti-FGF23 antibody is published for adult patients with X-linked hypophosphatemia rickets show promising results. This antibody therapy may be useful for patients with TIO [8].

4. CONCLUSION

TIO is a rare disorder that presents with muscle weakness, bone pain, and osteomalacia (and ultimately, if left untreated, fractures). Adult with these symptoms with persistent hypophosphatemia should be thoroughly evaluated to rule out TIO. As TIO mostly caused by benign mesenchymal tumour, complete cure is possible by surgical resection of tumour mass.

5. Conflict of Interest

The authors and planners have disclosed no potential conflicts of interest, financial or otherwise.

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