Diagnosis of TIO: Is Serum FGF23 Measurement always the Answer?

Sir,

A 48-year-old perimenopausal woman presented with recurrent fractures of both right and left femur, precipitated by minimal trauma while walking, one in May 2017 and another in June 2018. She had consulted local hospital for the same and was under management for primary osteoporosis based on DEXA scan reports showing a T score of less than -2.5. She was started on IV zoledronic acid 1 year ago, with precipitation of acute bone pains. Following this, 3 months later, she was started on Inj. teriparatide 20 µg daily. However, she had been worked up for metabolic bone disease, which was considered negative by her treating team. There was, however, a marginal elevation of PTH levels (80 pg/ml). Despite being on teriparatide, her bone pains had worsened which restricted her daily activity significantly; she was wheelchair bound for 2 months, at the time of presentation. On examination, while presenting at our center, the patient was nonambulant with severe proximal weakness and bone pains. Even slight involuntary movements associated with bone tenderness.

Further, we stopped her teriparatide for 1 week and evaluated her once again for the metabolic bone disease [Table 1]. Simultaneously, we performed the analysis of urine phosphorus and creatinine, which showed results consistent with phosphate wasting disorder. Fractional excretion of phosphate (FePi) was 22.05% in the setting of low serum phosphorus.

We strongly suspected an acquired phosphate wasting disorder. Considering the limited availability of FGF-23 marker in our institutions, she was referred for a 68-Ga DOTANOC PET CT scan on suspicion of any neuroendocrine tumor that could be the cause of tumour-induced osteomalacia (TIO). The scan reports revealed a local subcutaneous somatostatin receptor-expressing mass of 1.6 × 1.2 × 1.1 cm in the left Medial gluteal region [Figure 1]. A subsequent USG of the local area revealed a hypoechoic lesion in the same area.

Since the suspected TIO lesion was located subcutaneously coupled with the poor functional status of the patient, we proceeded to a quick excision of the said lesion under local anesthesia. Grossly the lesion was well circumscribed, 2 cm in maximum dimension which under light microscopy showed spindle cells in haphazard pattern, in a collagenous stroma [Figure 2a and b]. By Immunohistochemistry, the spindle cells were positive for Vimentin [Figure 2c] and few clusters were positive for CD68 [Figure 2d]. Based on Histomorphological and immunohistochemical features, the diagnosis of Benign Fibrous Histiocytoma was rendered. In most cases of TIO, small, benign, mesenchymal soft tissue tumors are major determinants for increased FGF23 level production in the body. Besides causing phosphaturia, FGF23 inhibits renal 1α-hydroxylase, the enzyme that converts 25-hydroxy vitamin D to its active form, 1,25-dihydroxy vitamin D.[1] Clinical features of bone pains, fatigue, proximal myopathy, and fragility fractures are noticed in most cases encountered.[2]

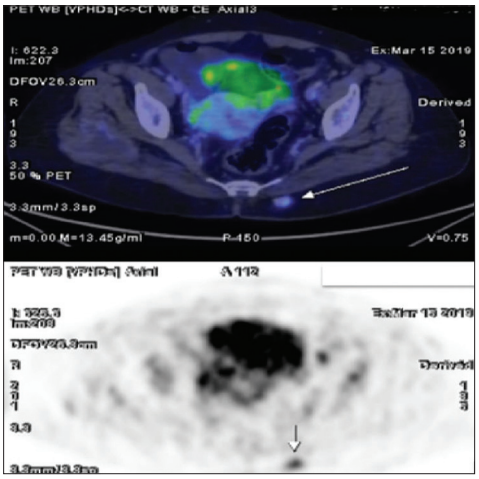

Figure 1: White arrows in both panels show a tracer avid enhancing lesion in the subcutaneous plane in the left gluteal region medially, measuring 12*15 mm with Max SUV 7.5

Table 1: Laboratory parameters during the course of the disease

Test	Before surgery		After surgery			
	3rd Mar 19	5th Mar 19	29th Mar 19 (1 week post-surgery)	13th Apr 19	12th May 19	12th Aug 19
Sr. Calcium (mg/dl)	9.5	10.4		10.1 mg/dl	9.95 mg/dl	8.7 mg/dl
Sr. Phosphorus (mg/dl)	1.99	2.11	5.78	4.86 mg/dl	5.0 mg/dl	4.2 mg/dl
Sr. alkaline phosphatase (IU/l)	96	86			152 IU/L	
Sr. creatinine (mg/dl)	0.85	0.9	0.72			
Urinary phosphorus (mg/dl)	27	24.4	12.4			
Urine creatinine (mg/dl)	52.4	29	48			
FePi (Fractional excretion of phosphate)	22.05%	35.8%	3.23%			

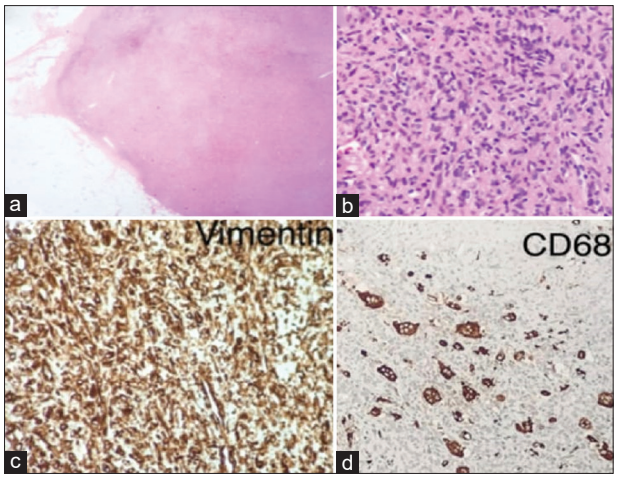

Figure 2: (a) Low power view showing cellular neoplasm with adjacent adipose tissue (H&E stain, ×40). (b) Higher magnification shows spindle-shaped cells with bland oval nuclei, minimal eosinophilic cytoplasm, arranged in vague storiform pattern (H&E stain, ×200). (c) Tumour cells strongly positive for Vimentin (×400). (d) Scattered clusters are positive for CD68 (×400)

The patient improved clinically post tumor resection and serum phosphorus levels returned to 5.78 mg/dl within a week of resection. Her proximal thigh muscle strength improved and the patient was able to walk without the aid of crutches, within a span of 3–4 months post resection. Considering her normalization of biochemical parameters and clinical improvement post tumor resection, a presumptive diagnosis of TIO was confirmed.

Although FGF-23 levels are considered the gold standard for diagnosing TIO, the differences in sensitivity of FGF-23 marker levels by various diagnostic methods like Kainos intact assay, immunotopics C-terminal assay, and immunotopic intact assay are considered a problem.[3] Added to this, few studies have reported normal FGF23 levels in clinically suspected TIO cases that were subsequently confirmed through 68-Ga DOTANOC scan and clinical improvement post tumor resection.[4] Prior studies have also shown DOTATATE PET/CT as a good initial step in functional imaging of clinically suspected TIO cases, wherein few cases have in fact shown near normal levels of FGF-23.[5] Our case suggests the possibility of diagnosing TIO using sound clinical judgment, assessment of biochemical parameters, and with the aid of sensitive diagnostic modalities like DOTANOC PET CT scan. We suggest that functional imaging modalities like DOTANOC PET CT may have a role in diagnosis as well as localization of these otherwise inconspicuous rare tumors.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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