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CASE REPORT

Ovarian Teratoma Causing Oncogenic Osteomalacia: An Instance of Serendipity

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Introduction

Tumour-induced osteomalacia (TIO) is a rare paraneoplastic manifestation of mesenchymal tumours, caused by the secretion of fibroblast growth factor 23 (FGF-23) which is a phosphatonin. Delayed recognition of this entity could potentially lead to severe osteomalacia and fractures involving the long bones, vertebrae or ribs. Precise localization of the tumour and complete excision of the same usually results in remarkable symptom relief and reversal of all biochemical abnormalities [1]. To the best of our knowledge, an ovarian teratoma presenting as TIO has not been reported in literature till date. Here, we present the case of a postmenopausal woman who presented with features of TIO secondary to an ovarian teratoma.

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Case Presentation

A 63-year-old postmenopausal woman, known to have type-2 diabetes mellitus for the past 11 years, presented to the endocrinology outpatient clinic with complains of aching pains all over the body, predominantly in her lower limbs for the last 6 months. Over the past 3 months, her symptoms had progressed to severe proximal myopathy with difficulty in ambulation, confining her to a wheel chair. She denied history of renal calculi, pancreatitis, fractures, small joint pain or swelling, sicca symptoms, heavy metal exposure or intake of indigenous medicines. Her diabetes mellitus was well controlled on oral anti-diabetic agents. She had been diagnosed with osteoporosis five years back and was on oral bisphosphonates with supplemental calcium and cholecalciferol. Her blood bone biochemistry was normal prior to the initiation of bisphosphonates. Clinical examination was significant for severe proximal myopathy.

Biochemical evaluation revealed fasting hypophosphatemia of 0.6 mg/dL(N: 2.5–4.6 mg/dL), phosphaturia with a TmP/GFR (tubular maximum for phosphate reabsorption, corrected for glomerular filtration rate) of 0.7(N: 2.5–4.5) and normal levels of total alkaline phosphatase of 94 U/L(N: 40–125 U/L). Serum creatinine, intact parathyroid hormone (iPTH) and 25(OH)vitamin D were normal. Radiograph of the pelvis revealed no evidence of pseudofractures and X-ray of the thoraco-lumbar spine showed diffuse osteopenia and osteophytes (Fig. 1). Due to persistently low levels of fasting phosphate, in the background of recent onset severe proximal myopathy, a possibility of tumour induced osteomalacia was considered. Estimation of FGF-23 revealed a high level of 3200 RU/mL (N 21–91). She was further subjected to a 68 Ga-DOTATATE PET CT (Gallium 68 dodecane tetra acetic acid tyrosine-3-octreotate—positron emission tomography-computerized tomography) which did not reveal any DOTA avid lesion. However, on the axial scans, there was noted to be a well-defined oval lesion

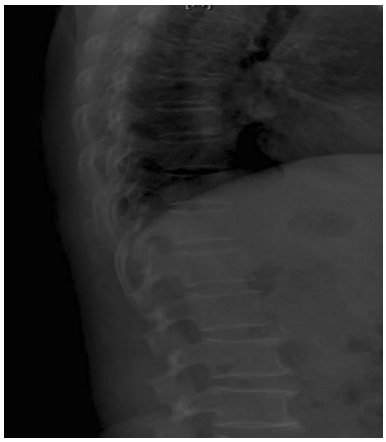

Fig. 1 X-ray of the thoraco-lumbar spine showed diffuse osteopenia and osteophytes

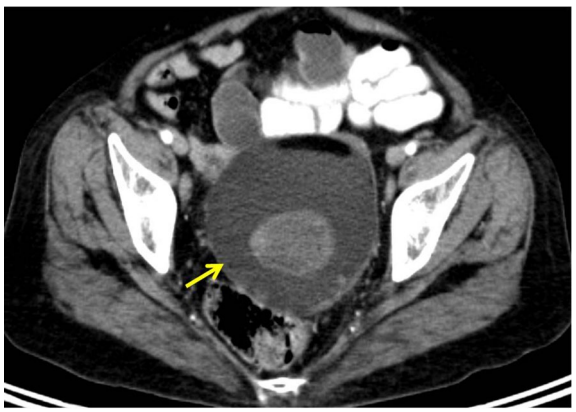

Fig. 2 Well-defined oval lesion measuring 9.2 × 8.8 cm in the pelvis, in the left adnexal region

measuring 9.2 × 8.8 cm in the pelvis, in the left adnexal region, with fat–fluid level and multiple rounded calcific densities along the wall of the lesion, and a heterogeneously enhancing mural nodule (Fig. 2). For symptom relief, she was initiated on oral neutral phosphate supplementation and calcitriol.

The patient underwent uneventful laparoscopic bilateral salpingo-oophorectomy and total excision of the left adnexal lesion. On histopathology, the adnexal lesion was reported to be a mature cystic ovarian teratomas (Fig. 3a), with the fibroblasts in the cyst wall showing immune-positivity for FGFR1(fibroblast growth factor receptor-1) (Fig. 3b). Following surgery, her symptoms gradually improved, serum phosphorus normalized and oral phosphorus and calcitriol were stopped. There was normalization of FGF-23 levels (88 RU/mL) on subsequent follow-up.

Discussion

Tumour-induced osteomalacia (TIO) is an uncommon paraneoplastic syndrome, mostly caused by small benign mesenchymal tumours that may be found at different sites. Tumours causing TIO can be further subdivided into four categories namely mixed connective tissue variant (phosphaturic mesenchymal tumour mixed connective tissue variant—PMTMCT), osteoblastoma-like variant, non-ossifying fibroma-like variant, and ossifying fibroma-like variant. Within the reported cases of TIO, tumours originate in soft tissues in 55% and bones in 40%. The various sites of tumour in decreasing order of frequency are the thigh and femur (22.7%), craniofacial region (20.7%), ankle and foot (8.8%), pelvis (8.2%), tibia and fibula (6.5%) and arms (6.5%). The less common locations are the vertebra, knee, hand, chest, abdomen, groin, perineum and gluteal regions [1]. TIO caused by an ovarian teratoma has not been reported till date. Patients typically present with history of chronic bone pain, fractures, and proximal muscle weakness. The occult nature of TIO delays its recognition, and the average time from the onset of symptoms to a correct diagnosis often exceeds 2.5 years. The biochemical hallmarks of TIO

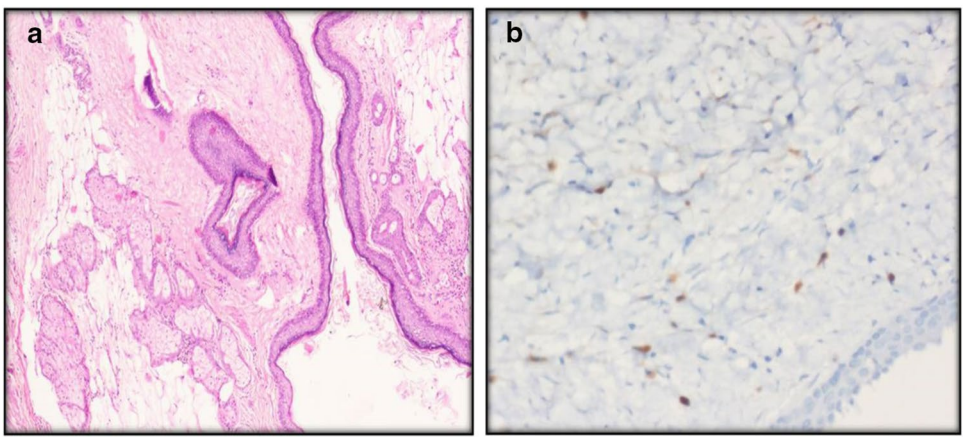

Fig. 3 **a** H&E X100 showing mature teratoma and **b** showing FGFR1 positivity on immunostaining

include low serum concentrations of phosphorus, elevated bone specific alkaline phosphatase, phosphaturia secondary to reduced proximal renal tubular phosphorus reabsorption, and frankly low or inappropriate normal levels of serum 1,25- dihydroxy vitamin D_3. Radiographic features of TIO include generalized osteopenia, pseudo fractures, and coarsened trabeculae. Elevated FGF 23 in an adult with recent onset hypophosphatemia with the above-mentioned biochemical picture favours the diagnosis of TIO. Serial physical examination with attention to palpable masses (especially in the extremities and the oral cavity) and appropriate imaging of the sites helps in localization of the tumour. Most mesenchymal tumours express somatostatin receptors, which can be diagnosed with whole body scan using radiolabelled somatostatin analogues. Although phosphorus supplementation and calcitriol give symptom relief, the definitive treatment for TIO is complete tumour resection. This results in rapid correction of the biochemical derangements and remineralization of bone. Fractionated stereotactic radiotherapy, CT-guided radiofrequency ablation, percutaneous ethanol ablation and cryoablation are the other treatment options available in clinical settings that preclude surgery. Burosumab(Anti-FGF23) antibody is a potential novel therapeutic option for FGF23-related TIO [2].

Although hypophosphatemic osteomalacia secondary to ovarian cancer has previously been reported by Lin et al.[3], this case is, to the best of our knowledge, the first report of an ovarian teratoma causing oncogenic osteomalacia. Oncogenic osteomalacia due to an ovarian teratoma is hitherto not described in literature. The ovarian mass was non-avid on the 68 Ga-DOTA PET CT. This is probably because of poor or absent expression of somatostatin receptors in differentiated ovarian tumours such as teratomas. The patient's symptoms and biochemical findings of hypophosphatemia resolved following surgical excision of the ovarian mass. There was normalization of FGF-23 levels following excision of the tumour. In addition, immunohistochemical staining for FGFR1 was also found to be positive on fibroblasts in the cyst wall. Phosphaturic mesenchymal tumour besides secreting FGF-23 also expresses FGFR1, due to the prevalence of FN1-FGFR1 fusion demonstrated in these tumours [4].

Thus, tumour-induced osteomalacia may manifest with varied presentations ranging from small obscure tumours in the head and neck region to anywhere in the distal extremities. As cases of oncogenic osteomalacia are increasingly reported in literature, the provisional list of causal tumours may get appended from time to time to include additional cases.

Declarations

Informed Consent Informed consent was obtained from the patient.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval Ethical approval by Institutional ethics committee.

Research Involving Human Participants and/or Animals This article does not contain any studies with animals performed by any of the authors.

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About the Author

Jinson Paul is a 33-year-old Medical Doctor who is a senior resident at Christian Medical College, Vellore, India which is a university affiliated tertiary care centre. He is a proactive doctor, with high investigative capacity especially in the field of bone disease. He maintains a good professional relationship, as well as an excellent doctor–patient relationship. He is also astute clinician and researcher. He is interested in taking on new challenges for the improvement of health.