Rare disease

'Tumour-induced osteomalacia'

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A 60-year-old man presented 2 years before his diagnosis with long-standing muscle cramping, progressive generalised weakness and chronic hip pain. The patient was found to have bilateral femoral neck pathologic fractures therefore, underwent reamed intramedullary nailing of both femurs. Laboratory studies showed hypophosphataemia. Bone marrow biopsy was negative for malignancy. Positron emission tomography demonstrated fludeoxyglucose uptake only in the posterior neck. Bone scan showed innumerable foci of increased activity throughout the skeleton consistent with pseudofractures seen in osteomalacia. Fine needle aspiration from the mass in the neck revealed a phosphaturic mesenchymal tumour of mixed connective tissue type. Resection of the mass in the neck resulted in resolution of generalised complaints with no evidence of recurrence with a follow-up of 12 months.

BACKGROUND

The clinical picture of tumour-induced osteomalacia usually presents as a diagnostic challenge and its recognition is delayed in most cases. The intent of our case report is to increase awareness of this condition as the clinical and laboratory abnormalities seen in tumour-induced osteomalacia are potentially reversible by tumour removal.

CASE PRESENTATION

A 60-year-old man presented 2 years before his diagnosis with long-standing muscle cramping, progressive generalised weakness and chronic hip pain. He was previously asymptomatic. The patient was a non-smoker and denied family history of malignancy.

INVESTIGATIONS

Labs showed low phosphorus at 0.5491 (normal 0.8075–1.4535 mg/dl), elevated alkaline phosphatase at 517 U/l (normal 0–140 U/l), chemiluminescence assay demonstrated increased intact parathyroid hormone at 101 ng/l (normal 10–75 ng/l) and normal 1,25-dihydroxyvitamin D (1,25-DHD) at 91 pmol/l. Complete blood count, monoclonal protein evaluation, tumour markers, thyroid, liver and kidney function tests were all normal. Urinalysis did not show glucosuria or aminoaciduria. The patient was found to have bilateral femoral neck pathologic fractures therefore underwent reamed intramedullary nailing of both femurs. Bone marrow biopsy was negative for malignancy. Positron emission tomography (PET) demonstrated fludeoxyglucose uptake only in the posterior neck (figure 1A,B). Bone scan (figure 1C) showed innumerable foci of increased activity throughout the axial and appendicular skeleton consistent with pseudofractures seen in osteomalacia. Fine needle aspiration from the mass in the neck revealed a phosphaturic mesenchymal tumour of mixed connective tissue type (figure 1D,E). Due to the suspicion of tumour-induced osteomalacia (TIO), a serum fibroblast growth factor 23 (FGF-23) level was obtained

which came back elevated at 575 RU/ml (normal <180 RU/ml). FGF-23 was measured by a commercially available immunometric enzyme assay from plasma.

DIFFERENTIAL DIAGNOSIS

Most of the dietary phosphate is absorbed in the duodenum and jejunum, and subsequently stored mainly in the bone; whereas only a dismal amount is extracellular. Circulating phosphate is filtered by the glomerulus, where approximately 90% is reabsorbed, until a threshold is reached, which signals that additional phosphate will be excreted in the urine.

Renal phosphate excretion is the primary mechanism to maintain phosphate equilibrium in our bodies; hence, it is not surprising that once hypophosphataemia is detected, the presence of renal phosphate wasting should be diagnosed, usually by calculating the percentage of tubular reabsorption of phosphate. Gastrointestinal causes of hypophosphataemia include total parenteral nutrition, refeeding syndrome and dietary deficiency of phosphate intake; albeit, they are all quite less common as a culprit than renal phosphate wasting as stated above. The differential diagnosis of hypophosphataemia is generally divided in inherited and acquired causes, the latter mainly comprised by TIO and Fanconi syndrome.¹ Fanconi syndrome differentiates from TIO in the way that FGF-23 is not elevated and it also presents a myriad of other abnormalities including glucosuria, aminoaciduria and proximal renal tubular acidosis. Most of the acquired forms of hypophosphataemia occur due to direct renal tubular damage by accumulation of an abnormal protein, a toxin or a drug as in heavy metal toxicity, aminoglycosides, chemotherapy, antiretrovirals and plasma cell dyscrasias. Other causes of renal phosphate wasting must be excluded as TIO is biochemically similar to some inherited forms of hypophosphataemic rickets nevertheless these entities usually present in childhood in the setting of a positive family history.² In general, the younger the patient at diagnosis, the more likely it has a genetic

Figure 1 Positron emission tomography (PET) demonstrated fludeoxyglucose uptake only in the posterior neck (A and B). Bone scan (C) showed innumerable foci of increased activity throughout the skeleton consistent with pseudofractures seen in osteomalacia. Fine needle aspiration from the mass in the neck revealed a high grade phosphaturic mesenchymal tumour of mixed connective tissue type (D and E).

cause. The adult onset and the negative family history in our case pointed towards TIO. Furthermore, the elevated level of FGF-23 and its subsequent normalisation following surgical excision of the tumour supports the diagnosis.^{3 4}

Additional laboratory testing might aid in establishing a diagnosis of TIO including 1,25-DHD, calcium and PTH. The latter is usually normal in TIO, although it could be high as in our case likely due to secondary hyperparathyroidism, which is an adequate response to low 1,25-DHD which in turn occurs due to elevated FGF-23.⁵ Conventional imaging techniques such as CT may fail to identify the tumours that are overexpressing FGF-23. Octreotide scintigraphy and PET have been used to localise such tumours.⁶

TREATMENT

Resection of the mass in the neck. No chemotherapy or radiotherapy indicated.

OUTCOME AND FOLLOW-UP

Resection of the mass in the neck resulted in normalisation of blood chemistry, FGF-23 and generalised complaints with no evidence of recurrence with a follow-up of 12 months, also significant improvement in the previously described diffuse abnormal osseous activity with mild residual activity in the inferior right lateral ribs was observed by bone scan.

DISCUSSION

Mesenchymal tumours are usually small, benign, slow growing, mostly situated at lower extremities (45%), facial skull and neck (27%) and upper extremities (17%).³ These tumours overexpress FGF-23 mRNA and have been classified as phosphaturic mesenchymal tumour mixed connective tissue type (PMTMCT) (70–80%), osteoblastoma-like

tumours, ossifying fibrous-like tumours and non-ossifying fibrous-like tumours.⁷ Tumour-induced osteomalacia is a rare acquired paraneoplastic syndrome characterised by overproduction of FGF-23 which is a phosphaturic agent that causes hyperphosphaturia and hypophosphataemia (renal phosphate wasting), associated with inappropriately normal or low levels of 1,25-DHD and it is typically seen with tumours of mesenchymal origin.

Diagnosis of this disease is often challenging as the presentation can be quite insidious while causing great disability which can be avoided by surgical removal of the inciting tumour.⁸

FGF-23 is produced by osteoblasts and it exerts strong inhibition on type IIa and IIc sodium/phosphate co-transport system in proximal tubules which promotes hyperphosphaturia that in turn triggers the constellation of symptoms seen in this syndrome. The clinical picture of TIO usually presents as a diagnostic challenge and its recognition is delayed in most cases. Indeed, the fact that many institutions are no longer adding phosphate to their routine chemistry evaluation might contribute to the delayed diagnosis of this often unrecognised entity. The intent of our case report is to increase awareness of this condition as the clinical and laboratory abnormalities seen in TIO are potentially reversible by tumour removal.

Learning points

- ▶ The clinical picture of TIO usually presents as a diagnostic challenge.
- ▶ The recognition of TIO is delayed in most cases.
- ▶ The clinical and laboratory abnormalities seen in TIO are potentially reversible by tumour removal.

Competing interests None.

Patient consent Obtained.

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