CASE REPORT

Osteolytic lesions: osteitis fibrosa cystica in the setting of severe primary hyperparathyroidism

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SUMMARY

A 58-year-old female patient presented with several weeks history of significant bilateral knee pain. Initial knee radiographs demonstrated lucencies of the bony cortex while extensive osteolytic lesions on a routine chest radiograph were suggestive of multiple myeloma or bony metastases. Biochemical investigation revealed primary hyperparathyroidism with renal insufficiency. A parathyroid adenoma was demonstrated on a neck ultrasound and sestamibi scan and subsequently confirmed by histology. We illustrate a case of primary hyperparathyroidism with osteitis fibrosa cystica and brown tumours which were initially mistaken for malignant disease.

BACKGROUND

Primary hyperparathyroidism (PHPT) is a relatively common endocrine disorder (25:100 000) caused by excessive and autonomous parathyroid hormone secretion most commonly resulting from a sporadic solitary parathyroid adenoma (85%–90%).^{1–3} It is most common in postmenopausal women and is frequently diagnosed in an outpatient setting due to incidental hypercalcaemia or during the investigation of osteoporosis and minimal trauma fracture.⁴ Familial parathyroid disorders such as multiple endocrine neoplasia (MEN) 1 and 2a and hyperparathyroid-jaw syndrome account for around 5% of PHPT, while parathyroid carcinoma represents <1%.³

The most common skeletal manifestation in PHPT is loss of cortical bone due to osteoclast activation with relatively preserved trabecular bone.² However, a more severe syndrome of skeletal loss is seen in osteitis fibrosa cystica (OFC), an uncommon disorder present in less than 2% of patients with PHPT in Western countries.² OFC is characterised by subperiosteal bone resorption, bone cysts (osteoclastoma; also known as brown tumours), lytic lesions and pathological fractures, especially of long bones.^{2,5–7}

Excessive parathyroid hormone leads to increased osteoclastic activity, predisposing to activation of the inflammatory cascade, which results in macrophage infiltration and fibrovascular tissue deposition.⁴ Foci of these inflammatory areas are known as brown tumours.¹ Brown tumours can be difficult to distinguish radiologically from true malignancy.

The cause for sporadic PHPT is unclear, but there are links to MEN1, hypoxanthine phosphoribosyl transferase and PRAD1 (cyclin D1) gene abnormalities.³ In addition, it appears that long-term lithium

use and thyroid ablation (for instance from irradiation or radioiodine) are risk factors.³

The reason why some patients go on to develop OFC and others do not is not fully understood. Some suggest that OFC is secondary to diagnostic delay while others suggest a role of disease in the context of low vitamin D/calcium stores leading to more severe manifestations.² A combination of the two would perhaps represent a reasonable explanation.

CASE PRESENTATION

A 58-year-old wheelchair-user female patient with a background of anxiety and long-standing lower limb weakness of unknown cause presented to hospital with a 2-week history of worsening bilateral knee pain with no history of recent trauma. The patient denied any infective symptoms, change in bowels, or nausea and vomiting, but did report worsening anorexia and associated weight loss of 5–10 kg over the preceding 2–3 months. The patient reported that her knee pain arose after performing leg exercises in bed. The patient's knee pain was presumed to be caused by osteoarthritis and she was admitted under the general medical team for further review.

The patient was socially isolated and lived with her elderly mother and sister. She was independent with activities of daily living, however, rarely left the house. The patient reported to placing herself in a wheelchair 18 months prior due to worsening lower limb weakness, however the cause of this weakness had not been investigated as the patient rarely sought medical review. The patient denied a history of smoking, alcohol or illicit substance use. There was no family history of malignancy or endocrine disorders.

INVESTIGATIONS

Admission knee X-ray (figure 1), chest X-ray (figure 2) and pelvic X-ray (figure 3) revealed widespread osteolytic lesions, with evidence of a chronic, ununited right humeral neck fracture and chronic, ununited bilateral neck of femur fractures with probable avascular necrosis of the femoral heads. Full blood picture demonstrated a normocytic anaemia (haemoglobin 96 g/L, mean corpuscular volume 86 fL) and mild thrombocytosis (platelets 444×10^9 /L). Inflammatory markers were elevated with an initial white cell count (WCC) of 16.0×10^9 /L and a C-reactive protein (CRP) of 24 mg/L. Both WCC and CRP reverted to normal the following day without intervention. Renal function and electrolytes were abnormal: creatine

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Figure 1 Lateral left knee X-ray demonstrating sclerotic focus (14 mm) in the distal femur and lucency of the anterior cortex of the tibia. Quadriceps enthesopathy, vascular calcification and joint space narrowing are also evident.

(156 $\mu\text{mol/L}$), urea (34.4 mmol/L), sodium (130 mmol/L), potassium (3.0 mmol/L) with normal bicarbonate (22 mmol/L). There was a mildly raised corrected calcium of 2.65 mmol/L (reference 2.20–2.55 mmol/L), phosphate (2.0 mmol/L) and alkaline phosphatase (341 U/L) with a normal vitamin D (79 nmol/L). Thyroid-stimulating hormone was elevated (4.75 mU/L) with borderline low fT4 (10 pmol/L). Repeat corrected calcium

Figure 2 Posteroanterior (PA) chest X-ray demonstrating extensive, predominantly lytic bony lesions throughout the visualised skeleton involving both clavicles, both humeri and multiple ribs bilaterally. Chronic ununited right surgical humeral neck fracture. Scoliosis of the thoracic spine (convex right) with mild distortion of the cardiac contour.

Figure 3 Pelvic X-ray with multiple lytic lesions throughout the pelvis and proximal femora. There are chronic, ununited, bilateral femoral neck fractures with probable avascular necrosis of the femoral heads. There is mixed lucency and sclerosis throughout the bony pelvis.

was 2.8 mmol/L and unfortunately ionised calcium was not reported due to laboratory or collection error. In the context of the clinical findings and laboratory results, malignancy with bony metastasis, multiple myeloma or hyperparathyroidism was suspected. Myeloma screen performed on day 2 of admission was negative with no paraprotein detected on serum immunofixation and normal serum levels of IgA, IgM and IgG. Serum beta-2 microglobulin was elevated (11.2 mg/L with a reference cut-off at 2.9 mg/L), however the context of inflammation and renal insufficiency was noted.

Parathyroid hormone level (PTH) was significantly elevated at 400 pmol/L (reference 1.5–8.0 pmol/L). Given the elevated calcium concentration, this is consistent with PHPT. The elevated PTH was confirmed by parallel assay performed at another laboratory. There was an elevated plasma C-terminal telopeptide of type 1 collagen (beta-CTX) at 2700 ng/L (reference 50–800 ng/L), urine N-terminal telopeptide of type 1 collagen (NTx) of 3655 bone collagen equivalents (BCE)/mol (reference <50 BCE/mol) and plasma procollagen type 1 N-propeptide (PINP) of 3326 ng/mL (reference 15–90 ng/mL), illustrating increased bone

Figure 4 Ultrasound of left inferior thyroid lobe demonstrating 23×14×16 mm mass lesion consistent with a parathyroid adenoma.

Figure 5 Sequential technetium dual-phase ^{99m}Tc -sestamibi parathyroid scintigraphy demonstrating a sestamibi-avid nodule posterior to the lower pole of the thyroid gland consistent with a parathyroid adenoma.

Figure 6 Dynamic whole body bone scan demonstrating innumerable metabolically active lesions throughout the skeleton with a right neck of humerus fracture and bilateral neck of femur fractures.

resorption and reactive formation. Serum gastrin and prolactin levels were within normal range, making a MEN1 diagnosis unlikely.

Neck ultrasound demonstrated a $23 \times 14 \times 16$ mm mass lesion within the left inferior thyroid lobe (figure 4), consistent with a parathyroid adenoma. A 7×6 mm left lower pole thyroid nodule was also evident, with no internal vascularity or definite calcification. Sequential technetium dual-phase ^{99m}Tc -sestamibi parathyroid scintigraphy (figure 5) revealed a sestamibi-avid nodule posterior to the lower pole of the thyroid gland consistent with a parathyroid adenoma. Renal ultrasound demonstrated small kidneys with poor corticomedullary differentiation consistent with chronic renal failure and multiple bilateral renal cysts.

Bone scan (figure 6) demonstrated innumerable metabolically active lesions throughout the visualised skeleton to support a diagnosis of OFC in the context of hyperparathyroidism. The right humeral neck and bilateral neck of femur fractures were again noted. Bilateral hand X-rays (figure 7) demonstrated extensive acro-osteolysis with extensive resorption in the middle and terminal phalanges, resorption of the terminal tufts and diffuse osteopaenia.

CT head (figure 8) revealed mandibular, maxillary and skull base sclerosis and expansion with multiple presumed brown tumours. There were no fibrotic jaw tumours.

Figure 7 X-ray right hand demonstrating extensive acro-osteolysis with resorption in a band-like pattern through the middle and terminal phalanges, as well as resorption of the terminal tufts which is virtually pathognomonic of hyperparathyroidism. There are brown tumours evident in the distal portion of the second metacarpal and second proximal phalanx. There is evidence of diffuse osteopaenia with extensive cortical lucency.

Dual-energy X-ray absorptiometry was ordered but could not be performed as the patient was unable to lie flat due to pain from multiple fractures.

DIFFERENTIAL DIAGNOSIS

Differential diagnoses for patients presenting with multiple bone lucencies include: metastatic carcinoma, non-Hodgkin's lymphoma, myeloma, fibrous dysplasia, hyperparathyroidism with brown tumours, benign or malignant vascular tumours, osteomyelitis and enchondroma.⁸ Factors to consider when assessing patients with multiple bone lucencies include: patient age, lesion size and number, margins and zone of transition (well-defined osteolytic, ill-defined osteolytic or sclerotic), anatomical location, periosteal reaction, cortical destruction and matrix calcification.⁸ Metastatic neoplasia and myeloma (plasmacytoma) should be considered in all patients over 40 years presenting with multiple bony lucencies.^{5,8} Our top differential diagnoses following initial assessment of this patient who presented with multiple bone lucencies and hypercalcaemia were bone metastases and myeloma, with hyperparathyroidism felt less likely given the extent of disease.

A thorough clinical history, examination and appropriate biochemical and radiological investigations assisted the authors to exclude malignant disease and diagnose PHPT with OFC and brown tumours.

TREATMENT

Neck exploration was undertaken by an experienced endocrine surgeon. An enlarged left inferior parathyroid gland (3389 mg) was resected. This enlarged gland was well encapsulated and demonstrated no macroscopic characteristics of malignancy. Left superior and right inferior parathyroid glands were inspected and were of normal appearance. A right superior parathyroid gland was not seen. Limited dissection of the thymus did not reveal ectopic parathyroid tissue.

Histopathological and immunohistochemical findings were consistent with a benign parathyroid adenoma. There was no severe nuclear atypia, no perineural or lymphovascular space invasions and a low mitotic index. Parafibromin expression was normal and protein gene product 9.5 (PGP 9.5) was negative.

The patient required intravenous calcium supplementation in the acute postoperative period, but was stabilised on oral calcium supplementation after 5 days.

OUTCOME AND FOLLOW-UP

The patient underwent extensive allied health assessment including dietetics, occupational therapy, physiotherapy and social work review. Orthopaedic review and opinion was sought, however the patient declined to undergo any orthopaedic interventions. The patient was reviewed by a psychiatrist for assessment and management of her anxiety.

Following her parathyroidectomy, the patient underwent a period of extensive rehabilitation in a specialised rehabilitation ward and could walk short distances with a frame upon discharge home.

The patient had not seen her general practitioner or endocrinologist in the 4 months following discharge.

DISCUSSION

OFC typically presents with bone pain, skeletal abnormalities and pathological fractures, especially of long bones, along with general features of hypercalcaemia.⁵ The radiological sequelae

Figure 8 CT head (transverse plane) through the mandible demonstrating diffuse expansion and deformity with multiple small, nodular, sclerotic foci representing brown tumours.

include diffuse osteopaenia, osteolytic lesions, pathological long bone fractures and resorption of terminal phalanges.^{5–7}

In our case, initial imaging including routine chest radiography showed widespread osteolytic lesions and pathological fractures. However, there is a wide differential for these findings, which in the context of cachexia and only mild hypercalcaemia, initially were felt to most likely represent metastatic lesions or myeloma rather than advanced PHPT.

The repeat corrected calcium showed a more significant elevation (2.80 mmol/L) with a raised parathyroid hormone level, in keeping with a PHPT. However, given the enlarged jaw and bilateral renal cysts, hyperparathyroid-jaw tumour syndrome remained an important differential.

Given the marked elevation of parathyroid hormone prior to surgery, there were also concerns regarding primary parathyroid malignancy, however, this was less likely given the chronicity of clinical symptoms. Histopathology and immunohistochemical findings revealed benign pathology and there was no evidence of multigland disease on neck exploration.

Learning points

- ▶ Primary hyperparathyroidism is a common endocrine disorder (25:100 000) due most commonly to a sporadic solitary parathyroid adenoma (85%–90%) and is most common in postmenopausal women.
- ▶ Severe manifestations of hyperparathyroidism are rare and include osteitis fibrosa cystica, brown tumours, pathological bone fractures and renal failure.
- ▶ Brown tumours are difficult to distinguish radiologically from malignant bone tumours.
- ▶ Clinicians need to exclude bone metastases (carcinoma, non-Hodgkin's lymphoma), myeloma and hyperparathyroidism in all patients presenting with hypercalcaemia and multiple bone lucencies, especially in patients aged over 40 years.

Prior to the 1970s, 15%–20% of patients with PHPT presented with bony changes and a further 50%–70% presented with renal manifestations.⁹ However, the availability of laboratory screening tests such as serum calcium and PTH level has made late manifestations of PHPT such as OFC, brown tumours and renal involvement increasingly rare in the developed world.^{4 6 7 9} Nevertheless, in populations where access to medical facilities is suboptimal and in socially isolated persons, OFC remains an important consideration in the diagnosis of osteolytic bone lesions.

Contributors LJ authored the case presentation, differential diagnosis, outcome/ follow-up and learning points sections and coauthored the investigation and treatment sections with WH and SR. MJ authored the summary and background, and coauthored the discussion section with WH and SR. WH and SR provided supervision, analysis and interpretation of data, drafting, and editing and coauthored the investigation, treatment, and discussion sections.

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