Rare disease

Primary hyperparathyroidism with classic and severe skeletal involvement

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Summary

A 63-year-old woman has had multiple repeated fractures. A diagnosis of primary hyperparathyroidism (PHPT) was made after she was found to be hypercalcaemic with an elevated level of intact parathyroid hormone (iPTH). Radiographs revealed classic and severe bone findings in PHPT, features which were common in the past but are thought to be rare at this modern age. She also had nephrolithiasis and osteoporosis. An enlarged parathyroid gland was seen on ultrasound and CT scan, and hyperfunction was demonstrated by scintigraphy. Parathyroidectomy was performed. Histopathologic analysis revealed a parathyroid adenoma. She developed the hungry-bone syndrome 7 days postoperatively, which resolved with administration of calcium and calcitriol.

BACKGROUND

This case is significant because (1) it illustrates the severe skeletal involvement seen in primary hyperparathyroidism (PHPT) that is rarely encountered at this modern age; (2) it demonstrates the work-up of a patient presenting with multiple fractures, hypercalcaemia and bony lesions; (3) it illustrates biochemical cure of PHPT after successful removal of a solitary parathyroid adenoma; and (4) it emphasises the recognition and appropriate management of the 'hungry-bone syndrome'.

CASE PRESENTATION

History and physical examination

A 63-year-old woman presented with repeated fractures at different sites over a period of 2 years, all sustained from low-impact-energy trauma. She first sustained a closed fracture of the left humerus for which closed reduction was done. This was followed 1 year later by a closed fracture of left leg, but she did not seek consult. She then developed a third fracture, this time on the left hip. On her latest consult at the emergency room, she sustained closed complete

Figure 1 Radiograph showing complete, transverse, displaced fractures of both femoral shafts (arrows). Note also the generalised osteopenia.

Figure 2 Moth-eaten appearance of the skull.

fractures of both femoral shafts after falling from a sitting position.

She complained of pruritus with no associated rashes. She denies having abdominal pains, and relatives did not observe any behavioural changes. She does not have haematuria, dysuria, nor flank pain. She also denies constipation, muscle pains, increased thirst or fatigue. Her falls were not associated with any loss of consciousness or seizures.

She is hypertensive with highest blood pressure (BP) of 160/100, usual BP of 130–140/80–90, without maintenance medications. She denies symptoms of hyperthyroidism. She denies steroid use. There is no similar illness in the family.

She had her menopause at age 48. She is G4P4 (4004). There was no intake of hormonal replacement therapy after menopause.

Patient was seen awake, conversant and coherent, yet confined in bed due to the fracture. BP was normal at 100/60, with heart rate of 70/min. She had a 1 cm nodule on the left thyroid lobe. There were no signs of hyperthyroidism or hypothyroidism. There was mass that was palpable at the area of the sternal notch.

Examination of the chest, lungs, heart and abdomen were normal.

Both thighs were grossly deformed but had no open wounds. There is no sign of phalangeal tuft resorption.

Figure 3 Lytic lesion of the proximal phalanx of the fourth finger, right hand (arrow).

INVESTIGATIONS

Diagnostic work-up Skeletal radiographs

The x-rays of lower extremities revealed complete, transverse, displaced fractures involving both femoral shafts (figure 1). There is an old fracture of the left femoral neck; the x-ray of upper extremities showed an old fracture with callus formation of the left humerus.

Skeletal survey radiographs revealed that the skull had a moth-eaten appearance (figure 2). There were lytic lesions in the proximal phalanx of the fourth finger on the right hand (figure 3), right distal femur and humerus (figures 4 and 5). The distal phalanges were not shortened. There is generalised osteopenia. There are no calcified urolithiasis seen.

The fractures were deemed pathologic because they occurred after low-impact-energy trauma, with the patient falling from a standing height in all instances. Differential diagnoses for pathologic fractures are metabolic bone disease and malignancy.

Biochemical tests

Central to the work-up of metabolic bone disease is the determination of serum calcium. This patient had persistently elevated levels of serum calcium ranging from 3.03 to 3.38 mmol/l (normal range: 2.12–2.54). She had elevated serum-ionised calcium at 1.65 mmol/l (normal: 1.10–1.35), coupled with an elevated level of intact parathyroid hormone (iPTH) at 820.2 pg/ml (normal: 15–65). Phosphorus was low normal at 0.968 mmol/l (normal: 0.801–1.600). These findings confirm the diagnosis of PHPT.

Ancillary tests

Serum electrophoresis was carried out and revealed no monoclonal component, which was consistent with a chronic inflammation type pattern. This rules out multiple myeloma which may also present with hypercalcaemia, fractures and bony lytic lesions.

A bone biopsy was made to check for bone malignancy. It only showed fragments of normal bone and skeletal muscle. No malignant cells were seen.

Abdominal ultrasound revealed a non-obstructing 0.6 cm lithiasis on the inferior calyceal region of the left kidney, and mild pelvocaliectasia on the right.

Urine calcium excretion was normal at 134.4 mg over 24 h. Serum creatinine was normal at 105 µmol/l.

Thyroid function tests were normal.

Dual emission x-ray absorptiometry revealed osteoporosis. T scores at various areas are as follows: lumbar spine 4.2, right femoral neck 3.7, left femoral neck 3.7 and right radius 4.8.

Imaging studies

To localise the source of excess parathyroid hormone, several imaging studies were performed. Neck ultrasound revealed a 4.3 × 2.9 cm complex mass at the lower pole of the right thyroid lobe with extension into the substernal area. The left thyroid lobe was enlarged and had a solid nodule measuring 1.6 × 1.1 cm.

CT scan of the neck and chest revealed a mass measuring 3.8 × 3.5 × 2.2 cm, seen inferior to the right thyroid lobe and extending into the thoracic inlet, probably of parathyroid origin. There were multiple osseous lucencies in the C6, C7

Figure 4 Lytic lesion of the posterior aspect of the right distal femur (arrow).

and T3 vertebral bodies; right pedicle of the T12 vertebral body; and the sternum and both humeral heads, compatible with changes in hyperparathyroidism. There was a $1.5 \times 1.31 \times 1.4$ cm hypoenhancing nodule in the left thyroid lobe. There was an incidental finding of left-ventricular cardiomegaly with a cardiothoracic ratio of 0.62.

Parathyroid scintigraphy using technetium-99m sestamibi revealed good uptake by the thyroid with appropriate clearance of the tracer, with the left thyroid lobe being prominent. There was a large (approximately 4×7 cm) focus of tracer accumulation in the substernal area which persisted until 2 h after injection of the radiotracer (figure 6). This was interpreted as a highly cellular mass in the substernal area consistent with a hyperfunctioning parathyroid adenoma.

DIFFERENTIAL DIAGNOSIS

PHPT secondary to a parathyroid adenoma, right, with multiple fractures, secondary osteoporosis and nephrolithiasis.

TREATMENT

Parathyroidectomy and left thyroid lobectomy were then carried out. Intraoperatively, there was a $5 \times 3 \times 1$ cm yellowish firm mass inferior to the right thyroid lobe extending into the substernal area (figure 7). This was excised and histologic analysis revealed parathyroid adenoma (figure 8). The left thyroid lobe was multinodular and enlarged to 5×6 cm. Histologic analysis revealed an adenomatous nodule.

Figure 5 Osteitis fibrosa cystica of the right humerus (arrow) and old fracture with callus formation of the left humerus (encircled).

Intact PTH done 48 h postoperation was already normal at 26.1 pg/ml. From a preoperative value of 3.38 mmol/l, corrected serum calcium progressively decreased to 2.95, 2.54, 2.23, 2.19 and 2.26 mmol/l at 6, 12, 24, 36 and 48 h postoperatively.

OUTCOME AND FOLLOW-UP

The patient was admitted to the intensive care unit after surgery. No arrhythmias occurred postoperatively. She developed clinical manifestations of hypocalcaemia (hungry-bone syndrome) on the 7th postoperative day: Chvostek's sign, carpopedal spasm, cramps and paraesthesias. Corrected serum calcium then was 1.89 mmol/l (normal: 2.12–2.54). She required intravenous calcium

administration, in addition to oral administration of calcium carbonate and calcitriol.

Serum calcium eventually normalised, and the hypocalcaemic symptoms were relieved after having been given 13 g cumulative dose of intravenous calcium gluconate administered from the 7th to 15th postoperative day and maintained on oral calcium carbonate 3 g/day and calcitriol 0.75 mg/day.

For the fractures, traction was applied to both legs which resulted in union and fracture healing. Intramedullary nailing was planned but was later deferred.

She was discharged 27 days postparathyroidectomy. She was sent home and for follow-up medication was prescribed the following: calcium carbonate 500 mg tablet, 2

Figure 6 Parathyroid scintigraphy with Tc-99m sestamibi demonstrating persistent radiotracer accumulation at the substernal area, compatible with a hyperfunctioning parathyroid adenoma.

Figure 7 Intraoperative finding of a parathyroid adenoma 5 × 3 × 1 cm in size, located inferior to the right thyroid lobe.

tablets three times a day; calcitriol 0.25 mg/tablet, 1 tablet three times a day; and alendronate 70 mg tablet, once a week.

On follow-up 1 year after parathyroidectomy, patient is already ambulatory with no recurrence of any fracture. She also does not manifest with symptoms of hypocalcaemia.

DISCUSSION

A solitary parathyroid adenoma is the most common cause of PHPT, causing up to 80% of cases. Other causes may be multiglandular adenoma, parathyroid hyperplasia or carcinoma.¹

The diagnosis of PHPT was straight forward in this case upon the demonstration of persistently high levels of serum

Figure 8 Microscopic examination showing a parathyroid adenoma on the right, separated by a fibrous capsule from the normal parathyroid gland on the left (100× magnification).

calcium, associated with a markedly elevated level of iPTH. Malignancy and multiple myeloma could also present with hypercalcaemia, fractures and lytic lesions, but these entities would have low levels of intact PTH.

There are only two entities which may present with hypercalcaemia and high iPTH. These are PHPT and familial hypercalcaemic hypocalciuria. The latter entity is characterised by hypercalcaemia being present early in life, with a similarly affected relative and a low urine calcium excretion, usually <100 mg in 24 h. Our patient did not have hypercalcaemia early in life, had no affected relative and had a urine calcium excretion of 134.4 mg over 24 h.

In the past (1930–1965), nephrolithiasis and skeletal disease were very common in PHPT, being present in as much as 57% and 23% of affected patients, respectively.² However, due to the advent of routine calcium measurement with the use of multichannel analysers, recent studies have shown that nephrolithiasis is only present in 18% of patients and none had skeletal disease.³ It is for this reason that this case is being reported because the classic complications of nephrolithiasis and skeletal disease are now considered rare entities.

Very striking in this case is the florid skeletal involvement. She presented with multiple repeated fractures in a span of 2 years involving the left humerus, right femoral neck and bilateral femoral shafts. The skeletal survey demonstrated the classic radiographic findings: new fractures of both femoral shafts, old fractures of the right femoral neck and left humerus, the moth-eaten appearance of the skull, the lytic lesions (osteitis fibrosa cystica) of a proximal phalanx, right humerus and distal femur, and generalised osteopenia. A CT scan was performed to determine the anatomic extent of the parathyroid, which also revealed

osseous changes in the vertebrae and humeral heads. The bone densitometry quantified the severity of osteoporosis, with a lowest T-score of 4.8 demonstrated at the right radius. Osteoporosis from PHPT affects the cortical bone more than cancellous bone. The lower T-score in the radius, a cortical-rich bone, supports this. In contrast, postmenopausal osteoporosis affects cancellous bone more than the cortical bone, and this would probably not manifest with low T-scores at the radius.

Renal involvement is considered the most common manifestation of PHPT, and the patient was not spared from this.¹ Though asymptomatic for renal disease, ultrasound revealed a non-obstructing nephrolithiasis on the left. Other renal manifestations are hypercalciuria (urine excretion >400 mg over 24 h) and nephrocalcinosis, both of which were not seen in this case.

Neuromuscular and cognitive complaints in the form of fatigue, weakness, depression and behavioural changes are also common, but these were not apparent in this case.

Hypertension and left ventricular hypertrophy have been associated with PHPT.¹ Interestingly, the patient has a history of hypertension, but this was controlled even without medications. Though the patient did not have symptoms of heart failure, x-ray demonstrated left ventricular cardiomegaly.

Surgery was indicated for this patient due to the skeletal and renal involvement. She also had a serum calcium level that was >1 mg/dl higher than the upper limit of normal (patient's value of 3.05 mmol/l equivalent to 12.2 mg/dl, compared to upper limit of normal which is 2.52 mmol/l or 10.08 mg/d). Had she been asymptomatic, the following are the indications for surgery as enumerated in the 2002 US NIH guidelines: serum calcium >1.0 mg/dl above normal, 24

h urinary calcium >400 mg, creatinine clearance reduced by 30%, T-score at any site of < 2.5 or age <50.¹

PHPT is cured by surgical removal of the source of excessive, unregulated, parathyroid hormone. Biochemical cure was demonstrated in this case by the marked return of intact PTH to normal 48 h after surgery (from 820.2 to 26.1 pg/ml).

The patient developed the 'hungry-bone syndrome' 7 days after surgery, manifesting with severe signs and symptoms of hypocalcaemia such as grade IV Chvostek's sign, carpopedal spasm and paraesthesias. This syndrome occurs because of extensive calcium deposition into the bone after the levels of PTH have already dropped, causing serum levels of calcium to decrease.⁴ This was managed with intravenous calcium gluconate, oral calcium carbonate and oral calcitriol.

She was sent home on oral calcium carbonate, oral calcitriol and oral alendronate. On outpatient follow-up, it is recommended that serum calcium and creatinine levels be assessed every 6 months coupled with annual repetition of bone densitometry.^{1 5}

Learning points

- ▶ This case demonstrates the severe skeletal involvement seen in PHPT that is rarely encountered at this modern age, such as moth-eaten appearance of the skull and lytic lesions of bone and osteitis fibrosa cystica.
- ▶ It also demonstrates the work-up of a patient presenting with multiple fractures, hypercalcaemia and bony lesions.
- ▶ This case also illustrates biochemical cure of PHPT after successful removal of a solitary parathyroid adenoma.
- ▶ Also, recognition and appropriate management of the 'hungry-bone syndrome' make this case worth reportable.

Competing interests None.

Patient consent Obtained.

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