CASE REPORT

Primary hyperparathyroidism from a probable ectopic parathyroid adenoma with severe skeletal disease and vitamin D deficiency

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SUMMARY

Primary hyperparathyroidism (PHPT) may lead to skeletal deformities, fractures and renal failure in symptomatic patients if untreated. We present a case of a 30-year-old woman presented with muscle weakness, weight loss, hypercalcaemia and a pathological fracture, eventually with rapidly progressive musculoskeletal disease. Subsequent biochemical, radiographic and scintigraphy findings were consistent with PHPT from an ectopic mediastinal adenoma, and concomitant vitamin D deficiency. The severe hypercalcaemia was adequately temporised with hydration, forced diuresis and intravenous bisphosphonates. Removal of the adenoma by video-assisted thoracoscopic surgery was contemplated; however, consent was withdrawn precluding histological confirmation. A review of literature shows the changing profiles of patients with PHPT, the uncommon occurrence of parathyroid adenomas in ectopic locations and possible association between severity of PHPT and vitamin D status.

BACKGROUND

Primary hyperparathyroidism (PHPT), most often due to solitary parathyroid adenomas, may result in a wide array of systemic complications such as secondary osteoporosis and pathological fractures due to bone resorption, and nephrolithiasis or acute renal failure due to hypercalcaemia. The initial presentation of these cases seems to vary widely according to geography. On the one end, up to 80% are asymptomatic with incidental findings of hypercalcaemia in areas with routine biochemical screening; on the other end, they may present with prominent musculoskeletal manifestations (45–79%) in areas where routine testing is not performed.¹

CASE PRESENTATION

Our case is of a 30-year-old woman with no known comorbidities and good baseline functional capacity, initially presenting with a 1-year history of progressive easy fatigability and generalised muscle weakness. In a few months, this rapidly worsened especially in the lower extremities, resulting in frequent falls during ambulation, and associated anorexia and an estimated weight loss of ~50%. She was eventually confined to her bed and was only able to ambulate with assistance. Owing to progressive symptoms, she was admitted at a private hospital where baseline laboratory workup showed hypercalcaemia. Further diagnostic examinations were suggested but were not performed to financial

constraints. After 1 month, while attempting to sit from a lying position, she experienced sudden severe pain over her right thigh worsened by movement, which prompted admission at our institution.

She was initially seen with stable vital signs, an intact sensorium, but was markedly undernourished. The rest of her initial physical examination was unremarkable except for a swollen, severely tender right thigh. Palpation of the neck did not reveal a goitre or discrete thyroid nodule. Plain radiographs revealed a closed, transverse fracture over the left femur (figure 1). Given the conditions of a pathological fracture and a history of hypercalcaemia, our initial differential diagnoses were an advanced malignancy with bone metastasis, multiple myeloma and PHPT.

Figure 1 Plain X-ray showing a transverse fracture of the right femur.

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INVESTIGATIONS

Additional workup revealed persistent hypercalcaemia up to 3.68 mmol/L (albumin-corrected), hypophosphataemia, normal renal function (by estimated-glomerular filtration rate, GFR) and an elevated intact parathyroid hormone (iPTH) measurement of 986.5 pg/mL (nv: 10–65). As part of baseline workup for pathological fractures, determination of 25-OH-D revealed vitamin D deficiency at 9.32 ng/mL (deficiency: <20 ng/mL).

A skeletal survey was also performed which showed generalised decrease in bone density, subperiosteal resorption, prominent trabecular markings and cortical thinning; mottled, 'salt-and-pepper' appearance of the cranial vault ([figure 2A](#)), loss in vertebral body height, marked thoracolumbar dextroscoliosis ([figure 2B](#)) and well-defined ovoid lucencies in the cortical regions of the radius and ulna were observed. A holoabdominal ultrasonogram showed medullary high-intensity echoes in both kidneys, suggestive of nephrocalcinosis.

After managing her severe hypercalcaemia (see treatment) and discharge, imaging and scintigraphy studies were performed for possible surgical planning. A neck and thyroid ultrasonogram was unremarkable. A parathyroid scintigraphy scan did not show any foci of tracer uptake in the neck region but revealed persistent tracer uptake over the right anterior haemothorax, which suggested an ectopic parathyroid adenoma ([figure 3](#)).

On her second admission a few months later for surgical planning, her anterior chest wall was noted to be grossly distorted with pectus excavatum deformity. A chest CT scan with intravenous contrast was performed showing inward bowing of the sternum and intrathoracic curving of the ribs, and worsening of her thoracic dextroscoliosis. After an extensive review, a well-defined, hypodense, 2.1×1.6×1.0 cm mass was located at the fourth intercostal space, right anterior hemithorax ([figure 4](#)). This was approximated to correspond to the ectopic tracer focus in the earlier Sestamibi scan.

DIFFERENTIAL DIAGNOSIS

On her initial presentation with a pathological fracture and hypercalcaemia, the main consideration was an unspecified malignancy with bone metastasis due to the marked cachexia and rapid progression of symptoms. Another main differential for the hypercalcaemia would be PHPT. With the baseline

laboratory examinations showing hypophosphataemia, normal renal function, suggestive radiological findings coupled with a highly elevated iPTH, the working diagnosis was revised to PHPT with severe hypercalcaemia, nephrocalcinosis and pathological fracture over the right femur. A markedly increased iPTH renders PTH-independent causes of hypercalcaemia such as malignancies or granulomatous disease very highly unlikely; this was further supported by negative findings on chest radiographs, and holoabdominal and pelvic ultrasonograms.

The rest of the diagnostic workup was directed towards localisation of the excess PTH source for surgical planning, hence the neck and thyroid imaging and scintigraphy scans were requested after her initial admission. This showed a probable parathyroid adenoma over the right anterior hemithorax based on persistent tracer uptake on scintigraphy corroborated by a chest CT scan with intravenous contrast showing a discrete hypodense lesion over the same area. The revised working diagnosis at this point was PHPT from an ectopic (mediastinal) parathyroid adenoma.

TREATMENT

During her initial admission for a pathological fracture and severe hypercalcaemia, she was initially managed by hydration with intravenous isotonic saline (3 L/day) along with oral fluids, followed by forced diuresis with furosemide 40 mg intravenous boluses, after 48 h, given after every litre of intravenous fluid. These measures were only partially able to lower her serum calcium to 3.08 mmol/L (from 3.68 mmol/L). Thus, intravenous bisphosphonate (pamidronate 60 mg) was administered as a slow infusion, which subsequently lowered her calcium to the upper normal range (2.43 mmol/L). She was then discharged with plans of localising the source of excess PTH and surgical intervention.

On her second admission for surgical planning, the rapid progression of the musculoskeletal deformities especially in the anterior chest wall resulted in mild resting dyspnoea and mild hypoxaemia on arterial blood gas analysis which required oxygen supplementation by nasal cannula. Hydration was continued and another dose of intravenous pamidronate was given due to recurrence of hypercalcaemia. The orthopaedic service was also consulted for possible bracing/support for the severe deformities.

Figure 2 Skeletal survey radiographs of the skull showing (A) 'salt-and-pepper' appearance and (B) marked dextroscoliosis of the spine.

Figure 3 Parathyroid scintigraphy scan (Tc-99 m sestamibi), anteroposterior (A) and lateral (B) views, showing persistent tracer uptake over the right anterior hemithorax (arrows).

Figure 4 Chest CT scan showing severe chest wall deformities and a well-defined, hypodense lesion at the right fourth intercostal space (arrow).

OUTCOME AND FOLLOW-UP

Removal of the identified ectopic parathyroid adenoma by video-assisted thoracoscopic surgery was planned after consulting with the thoracocardiovascular surgery service. The inherent risks of the procedure due to the compromised respiratory function versus the invariably deteriorating status due to persistent hypercalcaemia and high risk of subsequent pathological fractures were extensively discussed; however, the patient withdrew consent for surgery. She later requested discharge against medical advice. Communication with her relatives revealed her demise around 1 week from discharge. No autopsy was performed, precluding histological confirmation of the suspected ectopic parathyroid adenoma.

DISCUSSION

This case highlights the extreme end of the spectrum of PHPT, manifesting with severe skeletal deformities, pathological fractures and muscle weakness. The earliest reported cases of PHPT in the late 18th century mainly comprised patients presenting with severe skeletal deformities, fractures and asthenia, similar to our case.² Unfortunately, due to the paucity of knowledge concerning diagnostic workup and even more importantly management, many of the identified cases had unfavourable outcomes. A review on the evolving profiles of PHPT over the years clearly shows predominance of skeletal and urinary disease in the early 19th century. With the establishment of routine biochemical screening for serum calcium in the late 1960s and early 1970s, incidence rates were noted to increase along with the predominance of asymptomatic cases up to 80%.¹ Published local Philippine data on prevalence are lacking, where a large proportion of population with asymptomatic disease may remain undiagnosed due to the lack of routine biochemical screening.

The source of excess parathyroid hormone in this case was a probable adenoma with an unusual ectopic location at the anterior mediastinum. The parathyroid glands, normally four in number, can be divided into pairs of superior and inferior glands. The superior glands are typically found at the level of the cricoid cartilage, while the inferior glands are usually located in the posterolateral thyroid lobes. A review of 238 cases of surgically proven hyperparathyroidism showed 16% prevalence of ectopic glands, with 5 of 23 (22%) inferior glands found in the anterosuperior mediastinum. This resulted in an overall prevalence of a mediastinal adenoma of only 2%.³ Interestingly, the mean serum calcium levels among ectopic

parathyroid glands in this cohort were also noted to be significantly higher (12.2 mg/dL) than those in typical locations (11.5 mg/dL). Another 5-year review of 145 patients with PHPT showed 13 (9%) cases with adenomas in ectopic locations. Among these, only one case was reported to be found in the anterior mediastinum, with an overall prevalence of only 0.7%.⁴ Similarly, those with ectopic adenomas in this cohort had significantly higher serum calcium levels as well. Skeletal disease was also reported to be more common in these patients. In our institution, several published case reports of PHPT had adenomas located in the cervical region.^{5 6}

The case also highlights an interesting aspect in this disease, hinting on a possible association between vitamin D deficiency (as measured by 25-OH-D) and disease severity in PHPT. A review of 80 cases of confirmed PHPT grouped according to severity of vitamin D deficiency (by 25-OH-D levels) showed an inverse relationship between PTH and 25-OH-D levels. There was also a significant negative correlation between 25-OH-D levels and parathyroid adenoma size.⁷ Rao *et al* also looked into 147 cases of PHPT who underwent surgery and found a significant inverse correlation between PTH and 25-OH-D levels. When the patients were further classified into groups of high and low 25-OH-D levels, the parathyroid gland weights, adjusted serum calcium and PTH levels were significantly higher in the group with 25-OH-D <15 ng/mL.⁸ Another study compared 289 PHPT cases with age-matched controls and also found vitamin D deficiency or insufficiency to be more common in the former. With regard to parameters of disease severity, 25-OH-D had no significant relationship between adenoma size or fracture risk. There was only a weak positive correlation with femoral neck and forearm bone mineral density (BMD).⁹ The varying conclusions of the aforementioned studies may be due to differences in study design, populations being studied, cut-offs used for stratifying vitamin D deficiency and outcome measures for disease severity. Another limitation was their cross-sectional nature, which makes establishing causality difficult. At best, there appears to be an inverse relationship between PTH levels and vitamin D status in cases of PHPT; however, whether the vitamin D deficiency in this case existed prior to the onset of PHPT or was a consequence to worsening of the disease (ie, poor dietary intake, debility with limited sunlight exposure) seems unclear.

The rapid progression of her course and a missed opportunity for earlier diagnosis also emphasise the need to identify the aetiology of hypercalcaemia in any given patient. This will enable physicians to plan for definitive management in potentially correctable causes such as PHPT.

Learning points

- ▶ Major differential diagnoses in patients presenting with hypercalcaemia include primary hyperparathyroidism (PHPT) and malignancies.
- ▶ Most cases of PHPT are asymptomatic on diagnosis in areas where routine biochemical screening of serum calcium is performed.
- ▶ A small but significant proportion of cases of PHPT (9–16%) are due to adenomas in ectopic locations remote from the thyroid region.
- ▶ Vitamin D status appears inversely correlated with parathyroid hormone levels, with several studies suggesting increased severity of PHPT in vitamin D-deficient individuals. The relationship between vitamin D and PHPT is still poorly understood and needs more investigation.

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Competing interests None.

Patient consent Obtained.

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