INTRODUCTION

Primary hyperparathyroidism is the most common cause of PTH-mediated hypercalcemia, with an estimated prevalence of one to seven cases per 1000 adults. It occurs three times more often in females and typically in those older than 40 years old. Over the last several decades, there is a changing pattern towards asymptomatic presentation and incidental detection of hypercalcemia, likely due to increased health screening in developed countries.

Symptomatic hyperparathyroidism presenting with osteitis fibrosa cystica has become increasingly uncommon, with its incidence estimated to be under 2%. Multiple spontaneous tendon ruptures as the initial presentation of PHPT is even rarer, with such findings limited to case reports.3-6

While PHPT is a common endocrine condition in clinical practice, there are still unanswered questions in the management of severe PHPT which we would address in the discussion of this case.

CASE

A previously well 28-year-old male presented to the emergency department with acute pain and swelling of both knees and left elbow. Prior to this, he was walking on flat ground when both his knees buckled, causing him to fall onto his left side, after which he was unable to weight-bear.

As the initial radiographs did not show any fracture and dislocation, a magnetic resonance imaging (MRI) of bilateral knees and elbows were performed which showed left triceps, right infra-patellar and left quadriceps tendon ruptures as well as subperiosteal bone resorption of bilateral anterior distal femoral metaphysis.

Before this admission, he had no notable past medical history or medication use such as glucocorticoids or fluoroquinolones which may predispose to tendon ruptures. He did not smoke cigarettes or consume any alcoholic beverages. He worked as an office clerk. He did not participate in any high-impact sports. He did not have symptoms suggestive of hypercalcemia. There was no known personal or family history of hypercalcemia, fractures, renal calculi or endocrine tumor to suggest a hereditary cause of PHPT.

Clinical examination revealed signs of dehydration and swelling over his left elbow and bilateral knees, which were immobilised in a brace. No neck mass was appreciated.

Blood investigations revealed elevated serum calcium (3.85 mmol/L, normal range (NR) 2.10 to 2.60) and intact PTH (iPTH) (141.9 pmol/L, NR 1.3 to 7.6), low serum phosphate (0.48 mmol/L, NR 0.65 to 1.65) and concomitant vitamin D deficiency (7.2 µg/L, NR 30 to 100), in the setting of normal renal function (serum creatinine 95 umol/L with eGFR 94.1 ml/min/1.73m²) (Table 1). This biochemistry was highly suggestive of PHPT. Familial hypocalciuric
Because of the presence of severe hypercalcemia with extensive complications of PHPT and the need to exclude parathyroid carcinoma, early parathyroidectomy was indicated. He underwent preoperative localization of the lesion with a neck ultrasonography (US) and technetium-99m sestamibi parathyroid scan (Figure 3). Neck US showed a 2.7 cm x 1.8 cm x 1.8 cm right inferior parathyroid gland which demonstrated increased tracer uptake with delayed washout on the technetium-99m Sestamibi scan. These findings were consistent with a hyperfunctioning right inferior parathyroid lesion.

The patient's serum corrected calcium was closely monitored. He required a dose of zoledronate 4 mg IV within one week of pamidronate administration to keep serum corrected calcium <3.0 mmol/L (Figure 1). Vitamin D was judiciously replaced preoperatively to prevent worsening of hypercalcemia.

Further investigations revealed complications of hyperparathyroidism (Figure 2). Radiographs of hands and MRI of knees showed subperiosteal and subchondral bone resorption. Dual-energy X-ray absorptiometry (DEXA) scan showed low bone mineral density (BMD) for age, worst at the distal third radius with Z-score of -7.6. The Z-scores of left hip and lumbar spine were also low at -2.9 and -3.8, respectively. He also had extra-skeletal complications of bilateral calyceal calculi detected on computed tomography (CT) of the abdomen.

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As hereditary PHPT was still a possibility given his young age of presentation, pheochromocytoma was screened preoperatively (Table 2). Although the 24-hour urine normetanephrines were mildly elevated, this was derived from a urine volume of 8 liters. CT of the abdomen did not detect any adrenal or pancreatic mass suggestive of multiple endocrine neoplasia (MEN) 1 or 2A.

Due to the concern of suboptimal recovery associated with delayed tendon repair, the patient first underwent surgical repair of the right infrapatellar, left quadriceps and left triceps tendons, followed by a focused right inferior parathyroidectomy.
Intraoperative findings during the parathyroidectomy revealed an enlarged right inferior parathyroid gland with no visible invasion of surrounding tissues. The right superior parathyroid gland was normal looking. Intraoperative frozen section confirmed excision of the right inferior parathyroid gland and the intraoperative PTH decreased from 180.9 to 11.26 pmol/L 10 minutes after its excision. Histopathology subsequently reported a 2.0 cm x 1.2 cm x 1.0 cm parathyroid adenoma weighing 4.4 g, with no evidence of vascular or capsular invasion.

In anticipation of hungry bone syndrome (HBS), oral calcium carbonate 2.5 g TDS, calcitriol 0.5 µg BD and cholecalciferol 50,000 units weekly were started postoperatively. Intravenous calcium gluconate infusion was initiated when his serum calcium level dropped to 2.36 mmol/L. This was discontinued on the third postoperative day when he had stable normocalcemia on oral calcium carbonate 2.5 g TDS and calcitriol 1 µg BD (Figure 4). The oral medications

Table 2. Peri-operative screening investigations for MEN-1 and MEN-2A and genetic testing for Hereditary PHPT

| Parameter                          | Result | Normal reference range |
|------------------------------------|--------|------------------------|
| 24-hour urine volume, mL           | 8000   | 700 – 2000             |
| 24-hour urine metanephrine, nmol/day | 1168   | 400 – 1500             |
| 24-hour urine normetanephrine, nmol/day | 2632   | 600 – 1900             |
| 0800H serum cortisol, nmol/L       | 642    | 170 – 500              |
| IGF-1, µg/L                        | 115    | 85 – 236               |
| Gastrin, ng/L                      | <10    | 13 – 115               |
| Prolactin, mIU/L                   | 327.3  | 73 – 407               |

| Genetic Panel | Result | Normal reference range |
|---------------|--------|------------------------|
| MEN 1 gene    | Negative | –                     |
| RET gene      | Negative | –                     |
| CDKN1B gene   | Negative | –                     |
| CDC73 gene    | Negative | –                     |
| VHL gene      | Negative | –                     |
were gradually tapered to calcium carbonate 1.25 g BD and cholecalciferol 1000 units OM over the next three months during his inpatient rehabilitation.

Subsequent genetic testing did not detect any pathogenic variant in known susceptibility genes for hereditary PHPT (Table 2). Calcium carbonate and cholecalciferol were completely stopped 17 months after parathyroidectomy. Follow-up DEXA scans at the second and fourth years after parathyroidectomy continued to show improvement in BMD (Table 3).

Table 3. Bone mineral density (BMD) trend pre- and post-parathyroidectomy

|                | 2017   | 2019   | 2021   |
|----------------|--------|--------|--------|
| **Left hip**   |        |        |        |
| BMD, g/cm²     | 0.599  | 0.845  | 0.866  |
| Z-score        | -2.9   | -0.9   | -0.7   |
| **Left femoral Neck** |        |        |        |
| BMD, g/cm²     | 0.443  | 0.67   | 0.773  |
| Z-score        | -3.5   | -1.6   | -0.7   |
| **Lumbar spine** |        |        |        |
| BMD, g/cm²     | 0.553  | 0.863  | 0.852  |
| Z-score        | -3.8   | -1.0   | -1.1   |
| **Distal one-third radius** |        |        |        |
| BMD, g/cm²     | 0.41   | 0.515  | 0.524  |
| Z-score        | -7.6   | -5.6   | -5.4   |

The patient was young and had none of these risk factors. Tendon ruptures are uncommon injuries, usually occurring after trauma in patients older than 50 years. Spontaneous tendon rupture is even more rare, and its occurrence is often associated with chronic renal failure, diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus, fluoroquinolone or chronic corticosteroid use.1-6 Our patient was young and had none of these risk factors. Although spontaneous tendon ruptures have been reported in hyperparathyroidism, it is usually associated with
secondary or tertiary hyperparathyroidism related to chronic renal failure. Its occurrence in PHPT is extremely rare, with only a few case reports published in the literature.\(^3\),\(^6\)
In these patients, the tendon ruptures occurred mainly in the lower limbs. Our patient had multiple tendon ruptures affecting both upper and lower limbs. The pathophysiology of spontaneous tendon rupture in PHPT is not clear but postulated to be related to the pathological actions of chronic hyperparathyroidism. Hyperparathyroidism may induce excessive osteoclastic bone resorption at the bony cortex of tendon insertion sites or induce direct damage to tendons via dystrophic calcifications and depolymerization of tendon glycoproteins causing disruption to tensile strength. These mechanisms cumulatively cause weakening at the osteotendinous junction and predispose to tendon rupture following minimal trauma.\(^4\),\(^9\),\(^10\)

In patients presenting with spontaneous tendon ruptures, it is advisable that clinicians screen for risk factors such as chronic renal failure and diabetes mellitus, to review any history of corticosteroid or fluoroquinolone use and to rule out PHPT due to further implications on its management. The very marked elevation of PTH levels (often 10- to 20-fold increase) illustrating spontaneous tendon ruptures in PHPT in case reports as well as in our patient suggest that this rare complication may be related to the severity of PHPT.\(^3\),\(^4\) Hence, in patients with severe PHPT, the potential risk of spontaneous tendon ruptures should be considered. However, due to its rarity, there is insufficient data in the literature to advise on specific PTH, calcium or alkaline phosphatase (ALP) cut-off levels for identifying patients at risk of tendon rupture in PHPT. Nonetheless, with the severity and chronicity of hyperparathyroidism likely contributing to the pathophysiology of tendon ruptures, clinicians should aim to manage PHPT as promptly and optimally as possible.

Parathyroidectomy is the definitive treatment for PHPT. Successful parathyroidectomy has been associated with improvement in BMD, fracture risk, renal calculi formation and quality of life.\(^13\) Our preoperative strategy for this patient consisted of screening for associations with MEN syndrome, optimizing preoperative calcium and vitamin D levels, addressing risk factors for HBS, as well as planning for the surgical approach and extent of parathyroidectomy.

While there are no studies evaluating the safest preoperative serum calcium level, hypercalcemia may interfere with the action of anesthetic agents and increase the risk of cardiac arrhythmias. We opted to maintain preoperative serum calcium at <3.0 mmol/L.

As this patient’s pre-parathyroidectomy iPTH and ALP levels were elevated over tenfold, he was at risk of developing HBS. Postoperatively, he was confirmed to have a large right inferior parathyroid adenoma weighing 4.4 g. In literature, parathyroid adenomas >3.5 g have been associated with higher preoperative PTH and calcium levels as well as a greater risk for postoperative hypocalcemia.\(^12\)

A recent dual-center study from Singapore on 164 patients with PHPT who underwent parathyroidectomy showed median preoperative iPTH of 18.8 pmol/L, median corrected calcium of 2.7 mmol/L, median serum 25-hydroxyvitamin D of 20 ng/mL and median adenoma volume of 1 cm\(^3\). The study showed significant correlation between adenoma volume and preoperative iPTH levels and demonstrated that the pre-operative iPTH and ALP levels were significantly associated with the risk of developing HBS.\(^15\) Our patient had significantly higher pre-parathyroidectomy iPTH and corrected calcium levels, lower 25-hydroxyvitamin D levels and larger adenoma size compared to patients from the same population. This further emphasizes the atypical nature of our patient’s clinical presentation in a developed country and the risk for development of HBS.

Care was taken to reduce the risk of HBS for this patient by judiciously replacing vitamin D while balancing this with the risk of exacerbating hypercalcemia.

Vitamin D deficiency is common in PHPT. It is associated with higher PTH levels, more severe skeletal manifestations, possibly larger parathyroid adenomas and is also a risk factor for post-parathyroidectomy hypocalemia.\(^14\) The Fourth International Workshop on Asymptomatic Primary Hyperparathyroidism has recommended preoperative optimization of vitamin D to ≥20 ng/mL.\(^16\) However, there is no consensus on an ideal vitamin D replacement regimen in severe hypercalcemia. There is only one single-center, double-blinded randomized controlled trial with 46 patients addressing this concern. It showed that cholecalciferol 2800 IU daily for six months preceding parathyroidectomy did not significantly increase plasma or urinary calcium.\(^16\) Although there are other studies also supporting the safety of vitamin D replacement in PHPT, the mean serum calcium in these studies before replacement was less than 3.0 mmol/L.\(^17\),\(^18\)

A meta-analysis assessing the effect of vitamin D replacement in PHPT showed that although no patient developed hypercalcemic crisis, 2.2% of patients were found to have hypercalcemia exceeding 3.0 mmol/L.\(^19\) The current paucity of evidence on vitamin D replacement in severe hypercalcemia necessitates striking a fine balance between repleting vitamin D and mitigating the risk of aggravating hypercalcemia.

Although IV bisphosphate is used to manage severe hypercalcemia in those with PHPT, its role in the development of post-parathyroidectomy hypocalemia poses yet another controversy. The evidence assessing the effect of pre-parathyroidectomy bisphosphonate use and the development of HBS has mainly been in the form of observational studies and case reports. While most seem to suggest benefit with IV bisphosphate use and the attenuation of HBS, others implicate it in the exacerbation of hypocalemia after parathyroidectomy. There are, however, no specific recommendations on the use of bisphosphonates in the prevention of HBS.\(^20\)
Having a randomized controlled trial to evaluate the role of intravenous bisphosphonate administration in the prevention of HBS would be invaluable especially for those at high risk of experiencing this complication.

The ideal surgical approach in parathyroidectomy promotes a balance between achieving surgical cure and normocalcemia while minimizing the risk of persistent or recurrent disease and permanent hypoparathyroidism. The two main surgical approaches are bilateral exploration (BE) to allow four-gland exploration and minimally invasive surgery (MIS) for focused parathyroidectomy. Both approaches have shown good cure rates with few complications. The choice of surgical approach depends on preoperative localization imaging, risk of persistent or recurrent disease and expertise of the surgeon. While BE is more invasive, it is traditionally preferred in patients with hereditary PHPT, multi-gland disease, non-localizing or discordant preoperative imaging and after failure of MIS.

Genetic testing for hereditary PHPT has been recommended for patients under 40 years old. As patients with hereditary PHPT have increased risk of having multi-gland disease and recurrence of PHPT, preoperative genetic testing results may guide the patient and the surgeon on the extent of parathyroidectomy. Subtotal parathyroidectomy or total parathyroidectomy with auto-transplantation of parathyroid tissue has been recommended for those with MEN. The risk of permanent hypoparathyroidism, however, may be increased with these approaches compared to MIS. As such, MIS has occasionally been performed in carefully selected cases of hereditary PHPT where preoperative localization studies have confirmed single-gland involvement. This approach may have the benefit of reducing the risk of permanent hypoparathyroidism while preserving the contralateral side to facilitate future parathyroidectomy if PHPT recurs.

Nonetheless, prioritization for preoperative genetic testing has to be balanced with the risks of delay to curative parathyroidectomy, especially in severe PHPT. Regardless of intraoperative findings, genetic counseling should still be offered after parathyroidectomy to young patients to prognosticate the risk of recurrent PHPT and to determine the need to screen for other syndromic associations and cascade screening.

The reported recurrence rate of sporadic PHPT after parathyroidectomy may range from 1 to 14.8%, with recurrences occurring up to 20 years after parathyroidectomy. A single-center, retrospective study consisting of 196 patients with surgically cured sporadic PHPT were followed up for a median of 9.2 years. Recurrence occurred at a median of 6.3 years at a rate of 14.8%. Notably, 34.5% of recurrences occurred ten or more years after initial parathyroidectomy.

A more recent prospective study which included 261 patients with sporadic PHPT were followed up for a median of 60 months post-parathyroidectomy. The recurrence rate was 10.7% with mean time to recurrence of 77 months.

Although the risk of recurrence is greater in those with hereditary PHPT, these studies suggest that recurrence is not uncommon in sporadic PHPT and can still occur several years after curative parathyroidectomy.

In a young patient like ours, even though genetic testing did not reveal hereditary PHPT, it may be prudent to pursue long-term follow-up till further evidence advises on an alternative follow-up duration to monitor for the recurrence of PHPT.

CONCLUSION

This case report illustrates a rare and atypical initial presentation of PHPT in a developed country. In those with severe hyperparathyroidism and hypercalcemia, timely treatment is essential, with definitive parathyroidectomy being most ideal because of the likely pathophysiology implicated in spontaneous tendon ruptures in PHPT. Areas in PHPT management that still require clarification include defining a safe regimen of vitamin D replacement pre-parathyroidectomy; the role of pre-parathyroidectomy bisphosphonate use on the development of HBS; and the optimal duration of follow-up for monitoring for recurrence post-parathyroidectomy. Although this patient likely has sporadic PHPT due to a solitary parathyroid adenoma and has attained cure after parathyroidectomy, he will still benefit from continued monitoring for late recurrence.

Ethical Considerations

Patient consent was obtained before submission of the manuscript.

Statement of Authorship

Both authors certified fulfillment of ICMJE authorship criteria.

Author Contribution Statement

YJ and SSB prepared the original draft, reviewed and edited the manuscript, and prepared the data presentation. SSB supervised the research activity planning.

Author Disclosure

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