

Case report**Pathological fractures in teen and middle age women with primary hyperparathyroidism**Masliza Hanuni Ali¹, Hani Ajrina Zulkeflee², Wan Mohd Izani Wan Mohamed³, Tuan Salwani Tuan Ismail⁴**Abstract**

Primary hyperparathyroidism (PHPT) is a disease commonly seen in postmenopausal women. We report two cases of pathological fractures following trivial injuries in two different age groups; the middle and teen age group presented as PHPT due to parathyroid adenoma. PHPT usually presents with symptomatic hypercalcemia and target organ damage. Biochemical manifestations in both cases are similar i.e. hypercalcemia, elevated serum intact parathyroid hormone (iPTH), and mass in the parathyroid gland. Histopathological examination is consistent with parathyroid adenoma. We highlighted these two cases due to long delay before the PHPT diagnosis confirmed because of various investigations commenced in these patients to rule out other diagnoses.

Keywords: Primary hyperparathyroidism; pathological fracture; hypercalcaemia; brown's tumour

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PHPT is usually due to hyperplasia, adenoma or carcinoma of one or more parathyroid glands. Single parathyroid adenoma is the most common cause of PHPT. It is relatively rare in children compared to the adult and if it occurs in younger age, hereditary causes, specifically multiple endocrine neoplasia needs to be ruled out. It is characterized by mild to moderate hypercalcemia with elevated iPTH level. Patients may complain of fatigue, weak, anorexia or depress; or they may be completely asymptomatic.

Skeletal manifestation is often present in severe disease and rarely seen due to the early detection of the disease. The classical skeletal manifestation of PHPT is osteitis fibrosa cystica characterized as salt-and-pepper appearance in the skull, distal clavicular tapering, subperiosteal bone resorption, cysts and brown tumors¹. Parathyroidectomy is the gold standard treatment in PHPT especially for patient with bone and renal manifestation.

Table 1: Laboratory results before parathyroidectomy

Analytes			
Hb (g/dL)	8.7	8.4	10.6
WBC (x10 ⁹ /L)	8.6	7.2	6.85
Platelet (x10 ³ /L)	367	439	388
MCV (fl)	75.0	79.4	78.1
MCH (pg)	23.6	27.3	27.0
Calcium (mmol/L)	3.17	3.24	3.22
Albumin (g/L)	33	32	32
Globulin (g/L)	32	31	32
ALP (U/L)	719	652	814
Urea (mmol/L)	14.9	3.5	1.9
Creatinine (μmol/L)	111	105	99
Sodium (mmol/L)	132	141	144
Potassium (mmol/L)	4.4	3.6	3.6

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Table 2: Endocrine hormones level

Analytes	Prolactin (IU/L)	Cortisol (nmol/L)	Free thyroxine, FT4 (pmol/L)	Thyroid stimulating hormone, TSH (mIU/L)	Luteinizing Hormone, LH (IU/L)	Follicle stimulating Hormone, FSH (IU/L)
Level	212.2	247.7	12.7	1.6	2.9	7.4



Figure 1a



Figure 1b

Case 1

A 46-year-old Malay lady with underlying hypertension, presented with right thigh pain and inability to walk following a trivial fall. Further history of generalized weakness, lethargy, poor appetite and progressive loss of weight was noted for the past 5 months. She had a diffuse anterior neck swelling which moved with respiration. Lung examination revealed reduced breath sound and dullness on percussion at the right lower zone. Other systemic examination was unremarkable.

As shown in Table 1, she had hypercalcemia, elevated serum alkaline phosphatase, and hypochromic microcytic anemia. Renal and liver function were within the reference range. She had very high serum iPTH: 230.4 pmol/L (RR: 1.6-6.9 pmol/L). Other hormones levels were normal as shown in Table 2.

Radiography examination showed sub-trochanteric fracture of right femur with expansile osteolytic lesion. There was a generalized expansile osteolytic lesion with cortical thinning on skeletal survey (Figure 1a/b). Chest radiography revealed homogenous opacity over the right lower zone.

Figure 1a/b: Pathological lesion with expansile

osteolytic lesion and narrow zone of transition. Features suggestive of Brown tumor

Neck ultrasonography demonstrated multinodular goiter and a hypoechoic lesion at the left superior parathyroid gland. Computed tomography (CT) of the thorax, abdomen and pelvis showed right lower lobe collapse consolidation, atelectatic upper lobe of lung without lung nodules or mass, multiple bone lesions which was suggestive of metastasis, and bilateral renal calculi. Bronchoscopy examination revealed a nodular lesion at the right airway and narrowing of right lower lobe airway. Malignancy was excluded upon the histological examination of the lung biopsy.

In view of patient's presentation which mimicked the metastatic malignancy, thyroid gland biopsy was performed and medullary thyroid carcinoma was excluded. Finding in the core biopsy of the right proximal femur was consistent with brown tumor.

Patient was diagnosed with PHPT secondary to parathyroid tumor and was referred to surgical team for parathyroidectomy. Intra-operative monitoring of serum iPTH showed serial reduction in the iPTH concentration as shown in Table 3. Her serum calcium and iPTH returned to the normal range within one-

week post operation (Table 4). She recovered well and was discharged after day 10 post operation with further follow up at endocrine and orthopaedic clinic.

Table 3: Serum iPTH level before, intraoperative and after parathyroidectomy

Analyte	Before Parathyroidectomy			Intraoperative Parathyroidectomy			Before discharge
Serum iPTH (pmol/L)	230.4	138.4	133.3	49.2	14.2	10.1	0.9

Table 4: Laboratory results after parathyroidectomy

Analytes			
Calcium (mmol/L)	2.80	2.22	2.09
Albumin (g/L)	30	29	30
Globulin (g/L)	30	30	29
ALP (U/L)	583	637	952
Urea (mmol/L)	5.3	4.3	3.5
Creatinine (µmol/L)	90	95	93

Case 2

A 13-year-old girl with no known medical illness presented with 2 incidences of right and left femur fractures following a low-impact fall within 4 months. Her right femur fracture sustained earlier was treated by casting. On further questioning, she also experienced generalized weakness, lethargy, significant loss of weight (10 kg within 6 months), polyuria, constipation, and increased thirst in the past few months. She had no palpable mass in the neck and other clinical examinations were unremarkable.

Laboratory investigations demonstrated hypercalcemia, high serum ALP: 2869 IU/L and normal renal and liver function (Table 5). Hormonal evaluation showed high serum iPTH: 420pmol/L, and other hormones levels to exclude MEN syndrome were normal (Table 6).

Table 5: Laboratory results before parathyroidectomy

Analytes			
Hb (g/dL)	11.2	12.8	-
WBC (x10 ⁹ /L)	7.2	6.28	-
Platelet (x10 ³ /L)	351	330	-
MCV (fl)	89.5	87.5	-
MCH (pg)	30.0	30.3	-
Calcium (mmol/L)	3.64	3.60	3.48
Albumin (g/L)	37	36	37
ALP (U/L)	2869	-	2740
Urea (mmol/L)	1.0	1.1	-
Creatinine (µmol/L)	56	53	-
Sodium (mmol/L)	139	143	-
Potassium (mmol/L)	3.8	3.1	-

Radiography of the hip joint showed bilateral fractures at the neck of femur with expansile osteolytic lesions (Figure 2). Neck ultrasonography showed right solitary inferior posterior nodules consistent with parathyroid adenoma which is confirmed by Tc-99m sestamibi scan. Bilateral renal stones were found on abdominal ultrasound.



Figure 2: Bilateral hips fracture, thinning of cortex with osteolytic lesion

This patient undergone parathyroidectomy and intraoperative monitoring of serum iPTH demonstrated a serial reduction of the level, as shown in Table 7. She had an uneventful recovery and her serum calcium and iPTH level normalized within 2 weeks post-surgery (Table 8). Histopathological examination of the lesion confirmed a benign parathyroid adenoma. She was treated conservatively for her femur fractures in view of severe osteoporosis.

Discussion

PHPT with skeletal involvement normally presented with bone pain, skeletal deformities or pathological fractures as seen in both of our cases. Prolonged exposure to autonomous PTH secretion leads to cortical bone loss with relatively preserved trabecular bone². The imbalance between osteoblastic

Table 6: Endocrine hormones level

Analytes	Cortisol (nmol/L)	Free thyroxine, FT4 (pmol/L)	Thyroid stimulating hormone, TSH (mIU/L)	Luteinizing Hormone, LH (IU/L)	Follicle stimulating Hormone, FSH (IU/L)
Level	294.5	13.4	1.8	5.6	5.7

Table 7: Serum iPTH level before, intraoperative and after parathyroidectomy

Analyte	Before Parathyroidectomy		Intraoperative Parathyroidectomy		Before discharge		
Serum iPTH (pmol/L)	420	103	65.40 (0 min)	8.7 (10 min)	0.5	0.7	1.7

8: Laboratory results after parathyroidectomy

Analytes			
Calcium (mmol/L)	2.19	2.22	1.99
Albumin (g/L)	28	28	27
ALP (U/L)	4099	4010	3934
Urea (mmol/L)	0.7	1.6	2.1
Creatinine (μmol/L)	55	60	57
Sodium (mmol/L)	140	137	139
Potassium (mmol/L)	4.2	4.0	4.1

and osteoclastic activity results in bone resorption accompanied by fibrous replacement of the bone. This reduces bone mineral density (BMD) and conceivably escalates the fracture risk. According to the Canadian and international consensus of PHPT there is an increased risk skeletal fractures in PHPT patients reported by a few epidemiological studies¹.

Table

Brown tumor is difficult to distinguish clinically and radiographically from multiple myeloma, primary bone malignancy or bone metastases. As seen in our first patient, she underwent various investigations before the proper diagnosis was made. Brown tumor is a benign intraosseous lytic lesion consists of numerous giant cells with hemorrhagic infiltrates. It gains its name from the characteristic brown appearance of hemosiderin deposition. Histologically, brown tumor may be obfuscated with other giant cell lesions, i.e. giant cell granuloma, aneurysmal bone cyst or true giant cell tumor. Although it is not a true neoplasm, it can be locally invasive and thus mimic malignancies.

iPTH concentration in both cases were measured by second-generation PTH assays. Even though, third-generation PTH assays are now available and

measure only active iPTH, the diagnostic sensitivity of second and third-generation assays is similar in primary hyperparathyroidism and can be used to differentiate malignancy-related hypercalcemia (3). Elevated or inappropriately normal serum iPTH with hypercalcemia is suggestive of PHPT, while a suppressed iPTH level points to other causes of hypercalcemia and malignancy is the first on the list. Although PTH-related peptide (PTHrP) has similar homology to the N-terminal sequence of PTH, they are completely two different molecules with disparate structures. Hence, it will not cross react with serum iPTH assay.

During intraoperative iPTH (IOPTH) monitoring, baseline iPTH in both cases were taken after the induction of anesthesia prior to skin incision and repeated sample were taken at 10 minutes after gland removal(4). They successfully achieved a reduction of more than 50% of iPTH at 10 minutes post-excision than the baseline (Miami criterion) (5). Ideally, this assessment is made on third-generation iPTH assays because iPTH is rapidly metabolized after release. Thus, third-generation iPTH assays demonstrates a faster reduction in PTH levels compared to second-generation iPTH assays³. Other than used in assessing the adequacy of parathyroid resection, IOPTH levels can predict postoperative serum calcium concentration with the accuracy of 96%.⁶

The goal of treatment in PHPT is normalization of serum calcium and PTH with minimal associated morbidity. The only curative therapy for PHPT is surgical intervention⁷. In asymptomatic PHPT, parathyroidectomy increases BMD > 10% during the first decade⁸. A greater increment as much as 60 to 100% in BMD can be observed in symptomatic patients with severe bone involvement.⁹ A cohort

study among 674 PHPT patients in Denmark showed a normalization of fracture risk following parathyroidectomy.¹⁰In cases where surgical intervention is contraindicated, medical treatment can be given and the approach depends upon the goal of treatment, i.e. to reduce serum calcium concentration and/or increase BMD.

Conclusion

PHPT now is commonly recognized in early phase to the advancement in the analytical technologies. Skeletal manifestations of PHPT are relatively rare and diagnosis is often delayed as it may mimic primary or secondary malignant bone tumors. However, it is important to include PHPT in the differential diagnosis of pathological fractures to avoid unwarranted medical procedures.

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