

A Case Report of Primary Hyperparathyroidism with Severe Bony Involvement and Nephrolithiasis

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Abstract

Introduction: Although the majority of patients with primary hyperparathyroidism have a relatively asymptomatic benign disorder, there are patients who have a more aggressive disorder. **Clinical Picture:** We report a case of primary hyperparathyroidism presenting during pregnancy complicated by antepartum haemorrhage and severe prematurity. The diagnosis was made postpartum, when her problems rapidly progressed to result in severe neuromuscular weakness, bilateral pathological hip fractures as well as nephrolithiasis. **Treatment:** Surgical parathyroidectomy was performed. The underlying lesion was a large solitary parathyroid adenoma with cystic elements. **Conclusion:** Primary hyperparathyroidism is not an innocuous disease and can result in severe morbidity if left untreated.

Ann Acad Med Singapore 2001; 30:66-70

Key words: Nephrolithiasis, Parathyroid adenoma, Pathological fracture, Perinatal morbidity, Primary hyperparathyroidism

Introduction

Primary hyperparathyroidism is said to have evolved from a disease of “bones, stones and groans”,^{1,2} to one that is largely asymptomatic with a relatively benign course in the majority of patients.³ In a 1981 study, the incidence of radiologically detectable bone disease was found in 24% of patients⁴ but this complication is now considered rare.³ The incidence of renal stone disease from earlier studies quote figures ranging from 44% to 57%.^{5,6} More recently, however, this has decreased to between 10% and 25%.^{7,8}

In the 1930s, Albright and colleagues⁹ suggested that there was exclusivity of skeletal or renal involvement—that is, renal stone disease or bone involvement generally did not co-exist in the same patient. Pak and colleagues,¹⁰ however, disputed this and showed that there was no unique pathophysiological abnormality found in patients who develop nephrolithiasis. Silverberg and colleagues⁷ found that bone involvement in primary hyperparathyroid patients occurred to a similar extent in those with and without nephrolithiasis.

The cause of primary hyperparathyroidism is solitary parathyroid adenoma in 80% to 90% of patients.^{8,11} Most of these are small, usually weighing about 1 g but occasionally can be up to 10 g.

Case Report

A 31-year-old Chinese housewife was referred to the Endocrine Unit of the hospital with a problem of bilateral hip fractures after a minor fall. She had had bilateral hip replacements performed at the referring hospital. Postoperatively, she was noted to be unable to ambulate because of severe lower limb muscle weakness. Further investigations revealed hypercalcaemia and a high parathyroid hormone level. She was referred for further management.

Her problem started during her first pregnancy in April 1998. She developed severe persistent nausea and vomiting in the first trimester which continued, culminating in antepartum haemorrhage and premature delivery at 25 weeks gestation in August 1998. She also noted some constipation and progressive muscle weakness of all 4

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limbs. Incidentally, she had no complaints of polyuria or abdominal pain. During her antenatal visit with her obstetrician she was found to have a neck swelling which gradually increased in size over 15 months prior to her fracture. No further investigations were performed until postpartum. The baby weighed 540 g and was nursed in the neonatal special care nursery for several months. Further details regarding her pregnancy and infant were not available as she delivered in a neighbouring country. Postpartum, her muscle weakness progressed and she had difficulty walking, particularly up and downstairs.

She gave no history of renal calculi. There is no family history of similar illness.

In June 1999, she fell trying to walk down a curb and felt severe pain in both hips. She was found to have bilateral hip fractures. Postoperatively, investigations revealed hypercalcaemia and the diagnosis of hyperparathyroidism was made. She was subsequently referred to our Unit.

When seen in August 1999, she was chair-ridden, non-ambulant, pale, wasted, complained of considerable pain in the back particularly when moved. She was not dehydrated. Her blood pressure was 130/80 mmHg. A nodule was felt in the right side of the neck measuring 4 x 4 cm. Severe proximal muscle weakness of both upper and in particular, lower limbs were found. No other abnormalities were noted.

Investigations revealed haemoglobin 106 g/L, haematocrit 0.29, blood urea 5.0 mmol/L, creatinine 77 μ mol/L, electrolytes were normal, serum calcium repeatedly 3.1, 3.06, 3.64 mmol/L (normal 2.1 to 2.5), phosphate 0.6 mmol/L (normal 0.8 to 1.3), alkaline phosphatase 1286 IU/L (normal 35 to 110)—taken 2 months after the hip replacement. Parathyroid hormone taken at the same time as the serum calcium was 123; 142 pmol/L (normal 1.3 to 5.7).

Skeletal survey showed severe generalised osteopaenia with cortical thinning and coarse trabecular structure especially marked in the long bones. Skull X-ray (Fig. 1) showed a typical salt and pepper appearance. Pelvic X-ray (Fig. 2) demonstrated bilateral fracture neck of femur. No bone mineral density was performed.

Ultrasound kidneys revealed bilateral medullary nephrocalcinosis with multiple small renal calculi. Both kidneys were normal in size with normal echogenicity and good corticomedullary differentiation.

Computed tomographic (CT) scan of the neck with IV contrast (Fig. 3) revealed a large lobulated tumour mass in the mid and lower third of the R thyroid lobe, with necrotic areas seen within it measuring 5 x 4 x 3.5 cm. The tumour was compressing the right side of the trachea displacing it towards the left. It extended to the level just above the sternal notch. Appearances were more in keeping with a

thyroid malignancy than a parathyroid tumour. No cervical lymphadenopathy was seen.

A fine needle aspiration (FNA) cytology of the mass was performed on 19 August 1999 and 15 mL of blood tinged fluid was obtained. No colloid was identified in the fluid on gross inspection. Smears stained with May Grunwald Giemsa (MGG) showed a background of blood in which were seen clusters of epithelial cells with abundant cytoplasm, well-defined cell margins and vesicular, round or oval nuclei, giving an oxyphilic appearance (Fig. 4). There was focal marked variation in cell size with the presence of giant forms that showed pleomorphic nuclei and macronucleoli (Fig. 4). The cytological picture was compatible with a diagnosis of a parathyroid neoplasm.

The patient was hydrated with normal saline and IV pamidronate given in preparation for her surgery. Bilateral neck exploration was undertaken on 28 August 1999 by an experienced endocrine surgeon who performed a right thyroid lobectomy and parathyroidectomy. Histopathology of the tumour revealed a large parathyroid adenoma, measuring 7 x 5 x 4 cm in size and weighing 32 g. It was well-encapsulated and cut section showed a variegated picture with solid, cystic and haemorrhagic areas. Sections of the tumour stained with haematoxylin and eosin (H&E) showed a well-encapsulated lesion composed of parathyroid cells in organoid pattern with nests of tumour cells incompletely intersected by well-vascularised fibrous tissue septae (Fig. 5). The cells had abundant eosinophilic cytoplasm and vesicular nuclei. The variation in cell size and atypia seen in the cytological smears was reflected in the histological sections as well (Fig. 5). Multiple blocks of the tumour were studied for any evidence of capsular or vascular permeation and none was found. A histological diagnosis of parathyroid adenoma was made. The right superior parathyroid removed appeared unremarkable on gross and microscopic study. The parathyroids on the left appeared normal during operation and were left intact.

She developed hypocalcaemia on the first postoperative day with a nadir on the third postoperative day of 1.7 mmol/L. She was symptomatic, complaining of clinical paraesthesia and muscle cramps. This was treated with intravenous calcium gluconate followed by 1a calcidol 2 μ g daily and calcium carbonate 1300 mg twice daily. She continued to require replacement to maintain a normal calcium level even when last reviewed in June 2000 (9 months postoperatively).

Her muscle strength improved and by 7 months postoperation, she was able to walk unaided.

Discussion

It has been proposed that parathyroid hormone has a biphasic effect on bone with bone loss in the early phase

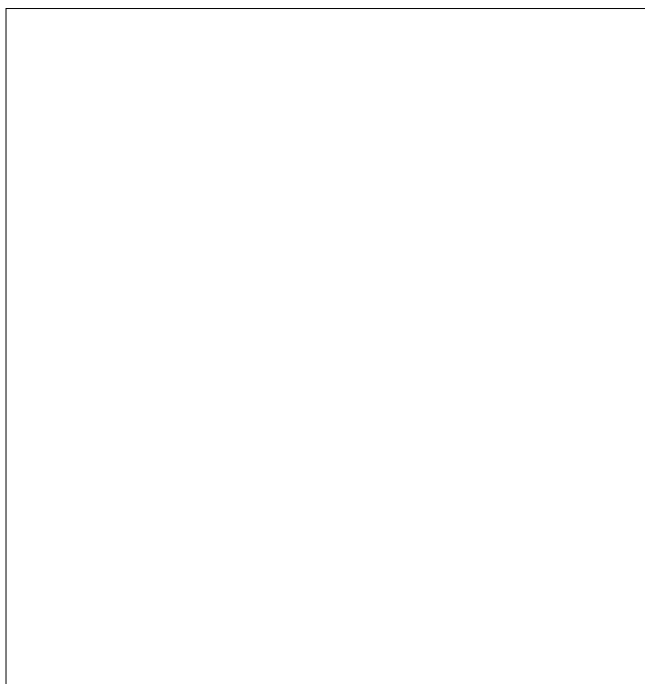


Fig. 1. Skull X-ray—Classic “salt & pepper” appearance.

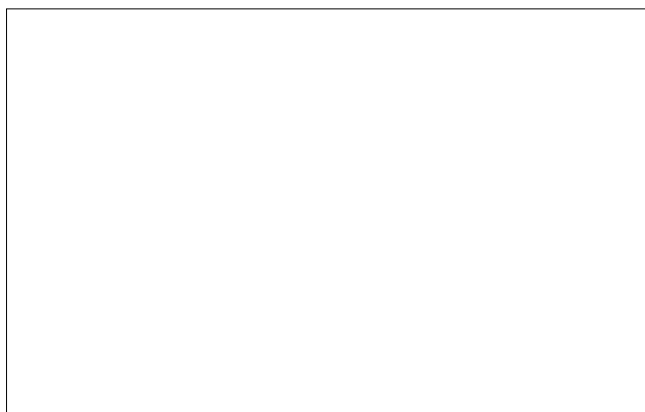


Fig. 2. Pelvic X-ray—Diffuse osteopaenia of the visualised pelvic bone with bilateral femoral neck fractures.

and no subsequent loss in the late phase of the disease.^{12–14} The bone disease most commonly associated with primary hyperparathyroidism is cortical bone demineralisation, particularly at the distal radius.^{15,16} An increase in fracture in the appendicular skeleton such as at the distal radius of 2- to 3.5-fold^{16,17} as well as at the ankle/foot¹⁷ has been found in subjects with primary hyperparathyroidism.

The femoral neck comprises equivalent proportions of cortical and cancellous bone and has been found to have an intermediate reduction in bone density as compared with the radius.⁷ Bilateral hip fractures were found to be extremely rare in a population-based cohort study conducted in Sweden by Larsson and colleagues.¹⁸ Their conclusion was that primary hyperparathyroidism was not a risk factor for hip fracture in women. The effect of primary hyperpara-

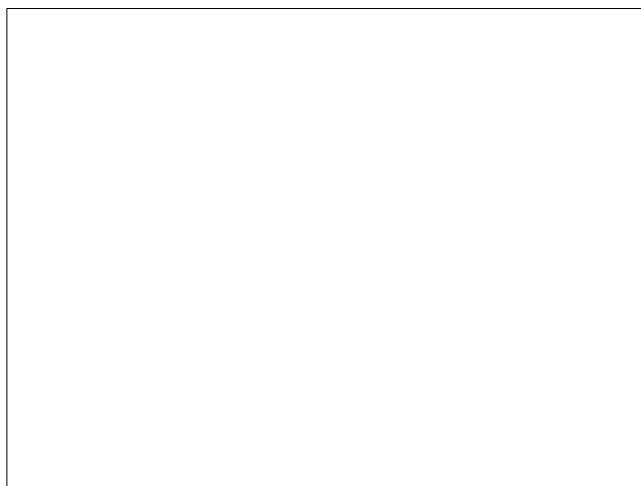


Fig. 3. CT scan neck—Necrotic, lobulated mass in the region of the lower pole of the right lobe of the thyroid gland.

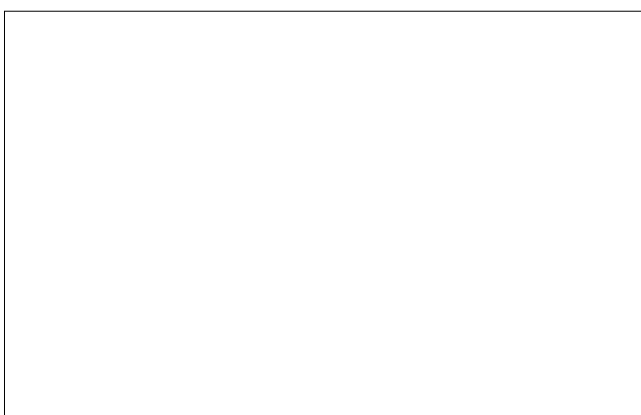


Fig. 4. FNA smear showing clusters of cells with abundant cytoplasm and round or oval vesicular nuclei (left) and focal marked nuclear atypia (right arrow). (Left — MGG x400; Right — MGG x200)

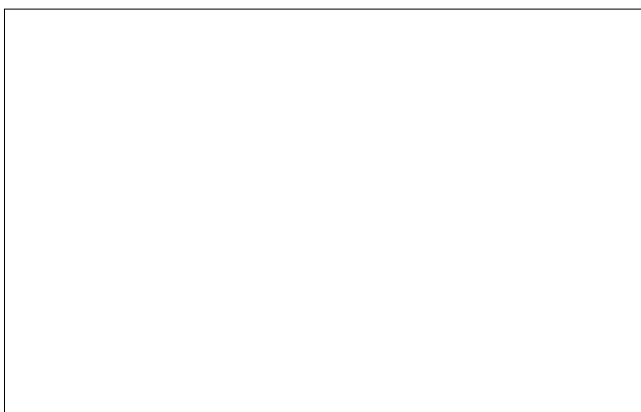


Fig. 5. Section from parathyroid adenoma showing well-vascularised tumour in organised pattern composed of cells of varying sizes with abundant cytoplasm and focal nuclear atypia (H&E x400).

thyroidism on vertebral fracture risk is unclear. The lumbosacral spine which has a large proportion of cancellous bone is thought to be relatively spared.^{15,19} However, an increased vertebral fracture rate has been reported in some

studies of a 1.5-fold increase²⁰ and 4.4% in subjects vs 0.2% in controls.²¹ On the other hand, those with mild degree of hyperparathyroidism have not been found to have an increased rate of vertebral fracture, 1.7% in subjects vs 2.8% in controls.²²

In postmenopausal women, Kenny and co-workers²³ reported more fractures (48% vs 25%) both in number and multiplicity of fractures, and height loss (50% vs 27%) in subjects than the control group.

Therefore, there is a higher risk for fracture in patients with primary hyperparathyroidism, in particular if they are postmenopausal, at the vertebrae and appendicular sites (distal radius, ankle/foot). The reason for the variable pattern and severity of skeletal involvement is multiple. Some of the likely factors are the severity of hyperparathyroidism as well as earlier diagnosis and identification of milder disease in recent years as a result of the easy availability of multichannel automated analysers. Other important factors are differences in host factors such as dietary calcium and its absorption from the gut and levels of activated vitamin D and phosphate balance. In this case, pregnancy which physiologically causes higher bone resorption was exacerbated by hyperparathyroidism resulting in the rare complication of bilateral pathological hip fractures after minor trauma.

This patient was also found to have nephrolithiasis and renal stone disease. Her renal function however, was still relatively normal. This is consistent with the study of Silverberg and colleagues,⁷ which demonstrated no differences in bone density between those with and without renal stone disease. They found that both bone and stone disease could occur together, as was demonstrated in our patient.

Our patient had a much larger parathyroid adenoma than is usually described. This was a solitary adenoma with areas of cystic change and haemorrhage. The treatment of choice was parathyroidectomy because of the severity of the clinical course, large palpable adenoma and the relative youthfulness of the patient. No preoperative localisation with thallium-sestamibi scanning was performed due to the following reasons: 1) the lesion was large; 2) the patient had no prior neck surgery; and 3) a diagnosis of parathyroid carcinoma was considered likely; therefore, prompt surgery was deemed necessary.

This patient had no evidence of multiple endocrine neoplasia.

Primary hyperparathyroidism is uncommon before the middle age and is even more rare during pregnancy. Thus, reports on pregnancies complicated by primary hyperparathyroidism are few. Reports from the early 1960s^{24,25} showed a 50% complication rate in such pregnancies including a 25% incidence of perinatal death

and 50% incidence of neonatal tetany. Pregnancy loss, perinatal morbidity and mortality were attributed to an increased incidence in spontaneous abortion, stillbirths, neonatal death and transient neonatal tetany lasting 3 to 5 months. The overall complication rate of stillbirths and neonatal deaths has been reported to decrease from 27% in the period of 1963 to 1975 to 5% in 1976 to 1990.²⁶ This reduction in mortality is thought to be due to earlier diagnosis of the disease therefore picking up milder hypercalcaemia, improved antenatal and perinatal care and more effective treatment of neonatal tetany. However, despite this improvement, only 54% of pregnancies from the 1976 to 1990 period resulted in term deliveries without tetany.²⁶

Some authors have suggested that there was a tendency toward low birth weight and intrauterine growth retardation.^{25,27} Marked premature placental calcification was reported in a woman with primary hyperparathyroidism by Graham and colleagues,²⁷ which was thought to be the reason for the premature delivery of a growth-retarded neonate.

Kelly²⁶ studied women who were treated medically compared to those who underwent surgery during their pregnancies. In those treated medically, 53% had neonatal complications and 16% neonatal deaths as compared to 12.5% neonatal complications and 2.5% neonatal deaths in those treated surgically. Thus, hyperparathyroidism in pregnancy is a serious disease. The treatment options for patients with progressive symptoms would be surgical parathyroidectomy during pregnancy for improved pregnancy outcome and only those women who are asymptomatic and have mild hypercalcaemia diagnosed in the third trimester can be managed medically and surgery postponed till postdelivery. This patient unfortunately did not have her hyperparathyroidism diagnosed during her pregnancy and she delivered prematurely at 25 weeks' gestation.

Conclusion

Our patient presents with severe and rare complications of primary hyperparathyroidism caused by a large solitary cystic parathyroid adenoma resulting in bilateral pathological hip fractures, neuromuscular weakness, nephrocalcinosis and nephrolithiasis. The presentation during pregnancy is uncommon but failure to recognise this during pregnancy has resulted in this case, prematurity and probable perinatal morbidity.

REFERENCES

1. Albright F, Reifenstein E C Jr. The parathyroid glands and metabolic bone disease. Baltimore: Williams & Wilkins, 1948.

2. Cope O. The story of hyperparathyroidism at the Massachusetts General Hospital. *N Engl J Med* 1966; 274:1174-82.
3. Bilezikian J P, Silverberg S J, Gartenberg F, Kim T S, Jacobs T P, Siris E S, et al. Clinical presentation of primary hyperparathyroidism. In: Bilezikian J P editor. *The Parathyroids: Basic and Clinical Concepts*. New York: Raven Press, 1994:457-70.
4. Scholz D A, Purnell D C. Asymptomatic primary hyperparathyroidism: 10-yr prospective study. *Mayo Clin Proc* 1981; 56:473-8.
5. Peacock M. Renal stone disease and bone disease in primary hyperparathyroidism and their relationship to the action of PTH on calcium absorption. In: Talmadge R, editor. *Calcium Regulating Hormones*. Amsterdam: Excerpta Medica, 1975:78-81.
6. Broadus A E, Horst R L, Lang R, Littledike E T, Rasmussen H. The importance of circulating 1,25 (OH)₂ vitamin D in the pathogenesis of hypercalciuria and renal stone formation in primary hyperparathyroidism. *N Engl J Med* 1980; 302:421-6.
7. Silverberg S J, Shane E, Jacob T P, Ethel S S, Gartenberg F, Seldin D, et al. Nephrolithiasis and bone involvement in primary hyperparathyroidism. *Am J Med* 1990; 89:327-34.
8. Browder W, Rakinic J, Schlechter R, Krementz E. Primary hyperparathyroidism in the seventies. A decade of change? *Am J Surg* 1983; 146:360-5.
9. Albright F, Aub J C, Bauer W. Hyperparathyroidism: a common and polymorphic condition as illustrated by 17 proven cases from one clinic. *JAMA* 1934; 102:1276-87.
10. Pak C Y C, Nicari M J, Petersen R, Zerwekh J E, Snyder W. Lack of unique pathophysiologic background for nephrolithiasis in primary hyperparathyroidism. *J Clin Endocrinol Metab* 1981; 53:536-42.
11. Heath H, Hodgson S F, Kennedy M A. Primary hyperparathyroidism: incidence, morbidity and potential economic impact in a community. *N Engl J Med* 1980; 302:189-93.
12. Rao D S, Wilson R J, Kleerekoper M, Parfitt A M. Lack of biochemical progression or continuation of accelerated bone loss in mild asymptomatic primary hyperparathyroidism: evidence of biphasic disease course. *J Clin Endocrinol Metab* 1988; 67:1294-8.
13. Warner J, Clifton-Bligh P, Posen S. Longitudinal changes in forearm bone mineral content in primary hyperparathyroidism. *J Bone Miner Res* 1991; 6(suppl 2):S91.
14. Richardson M L, Pozzi-Mucelli R S, Kanter A S, Kolb F O, Ettinger B, Genant H K. Bone mineral changes in primary hyperparathyroidism. *Skeletal Radiol* 1986; 15:85-95.
15. Silverberg S J, Shane E, de la Cruz L, Dempster D W, Feldman F, Seldin S, et al. Skeletal disease in primary hyperparathyroidism. *J Bone Miner Res* 1989; 4:283-91.
16. Larsson K, Lindh E, Lind L, Persson I, Ljunghall S. Increased fracture risk in hypercalcaemia: Bone mineral content measured in hyperparathyroidism. *Acta Orthop Scand* 1989; 60:268-70.
17. Melton L J, Atkinson E J, O-Fallon W M, Heath H. Risk of age-related fractures in patients with primary hyperparathyroidism. *Arch Intern Med* 1992; 152:2269-73.
18. Larsson K, Ljunghall S, Krusemo U B, Naessen T, Lindh E, Persson I. The risk of hip fractures in patients with primary hyperparathyroidism: a population-based cohort study with a follow-up of 19 years. *J Intern Med* 1993; 234:585-93.
19. Block M A, Dailey G E, Muchmore D E. Bone demineralisation, a factor of increasing significance in the management of primary hyperparathyroidism. *Surgery* 1989; 106:1063-9.
20. Kochersberger G, Buckley N J, Leight G S, Martinez S, Studenski S, Vogler J, et al. What is the clinical significance of bone loss in primary hyperparathyroidism? *Arch Intern Med* 1987; 147:1951-3.
21. Dauphine R T, Riggs B L, Scholz D A. Back pain and vertebral crush fractures: an unrecognised mode of presentation for primary hyperparathyroidism. *Ann Intern Med* 1975; 83:365-7.
22. Wilson R J, Sudhaker R, Ellis B, Kleerekoper M, Parfitt A M. Mild asymptomatic primary hyperparathyroidism is not a risk factor for vertebral fractures. *Ann Intern Med* 1988; 109:959-62.
23. Kenny A M, MacGillivray D C, Pilbeam C C, Crombie H D, Raisz L G. Fracture incidence in postmenopausal women with primary hyperparathyroidism. *Surgery* 1995; 118:109-14.
24. Ludwig G D. Hyperparathyroidism in relation to pregnancy. *N Engl J Med* 1963; 267:637-42.
25. Wagner G, Transbol I, Melchior J. Hyperparathyroidism and pregnancy. *Acta Endocrinol* 1964; 47:549-64.
26. Kelly T R. Primary hyperparathyroidism during pregnancy. *Surgery* 1991; 110:1028-34.
27. Graham E M, Freedman L J, Forouzan I. Intrauterine growth retardation in a woman with primary hyperparathyroidism. *J Reprod Med* 1998; 43:451-4.