Primary hyperparathyroidism in Hong Kong: an analysis of 44 cases

FKW Chan, SC Tiu, KL Choi, TK Au Yong, LF Tang

Primary hyperparathyroidism is increasingly being diagnosed subsequent to the detection of hypercalcaemia using multichannel auto-analyser screening. This paper provides a local picture of the clinical presentation and management of primary hyperparathyroidism. A retrospective review was conducted of 44 patients with primary hyperparathyroidism who were treated at the Queen Elizabeth Hospital between January 1987 and July 1996. Twenty-five (56.8%) of the patients were asymptomatic. Only three (6.8%) patients gave radiograms that had features indicating primary hyperparathyroidism; seven (15.9%) had renal stones. The patients underwent one or more of the following localisation procedures: computerised tomography, ultrasonography, thallium-technetium subtraction scanning, and technetium Tc 99m sestamibi scanning. The latter method was the most sensitive (64.3%). Ten adenomas that could not be localised by any of these procedures were successfully removed during surgery. Surgery was successful in 94.4% of cases and surgical outcome was comparable to that reported in the literature.

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Introduction

Primary hyperparathyroidism is caused by the excessive, abnormally regulated secretion of parathyroid hormone (PTH) from one or more adenomatous or hyperplastic parathyroid glands. The major actions of PTH are to mobilise calcium from bone, to conserve calcium in the kidneys, and to indirectly increase gastrointestinal calcium absorption. An increased PTH level leads to one of the major biochemical hallmarks of the disease—hypercalcaemia. Primary hyperparathyroidism is the commonest cause of hypercalcaemia in the out-patient setting. Since 1975 in the United States, the widespread use of multichannel serum chemistry auto-analysers has coincided with a dramatic increase in the incidence of primary hyperparathyroidism.[1] Not only has there been an increase in the incidence of the disease, there has also been an evolutionary change in the presentation of the disease: from the classical 'bone and stone' presentation to an asymptomatic one.

In Hong Kong, the first auto-analyser was installed in 1985. Based on auto-analyser results, Shek et al[2] conducted a study of blood samples obtained from the local in-patient population in 1990, and detected an incidence of primary hyperparathyroidism of 1:3000. There have been no data on the changes in the incidence of primary hyperparathyroidism among the local population since the installation of auto-analysers. We are, however, encountering an increasing number of patients with primary hyperparathyroidism at the Queen Elizabeth Hospital (QEH)—a regional hospital which has 1900 beds. The frequency of parathyroidectomy at the QEH increased from one per year in 1987 to one per month in 1996.

Subjects and methods

A retrospective review was conducted of the 44 patients who were treated for primary hyperparathyroidism at the QEH between January 1987 and July 1996. The diagnosis was based on the finding of an elevated serum calcium concentration, an elevated serum parathyroid hormone level, and the exclusion of other causes of

Queen Elizabeth Hospital, 30 Gascoigne Road, Kowloon, Hong Kong:
Department of Medicine
FKW Chan, FHKCP, FHKAM (Medicine)
SC Tiu, FRCP, FHKAM (Medicine)
KL Choi, FHKCP, FHKAM (Medicine)
Department of Nuclear Medicine
TK Au Yong, MSc
Department of Surgery
LF Tang, FRCS, FHKAM (Surgery)

Correspondence to: Dr FKW Chan

hypercalcaemia. None of the patients had a history of preceding secondary hyperparathyroidism. The median duration of follow-up was 40 months. Of the 44 patients, three refused surgery and one had medical contra-indications to surgery. Parathyroidectomy was performed for 40 patients; three patients defaulted postoperative follow-up. These three patients, and the four who did not receive surgery, were excluded from the analysis of various preoperative procedures and their surgical outcome.

Parathyroid hormone levels were measured by an immunochemiluminometric assay that detected intact hormone and which had been used at the QEH since 1993. Before 1993, radioimmunoassay was used to measure PTH levels by detecting N-terminal or mid-region segments of PTH. Preoperative localisation procedures included ultrasonography, computerised tomography (CT), thallium-technetium (Th-Tc) subtraction scanning, and technetium Tc 99m–labelled sestamibi scanning. For CT performed before August 1994, conventional scans were obtained by using a model GE8800 CT scanner; thereafter, spiral CT scans were performed. Thallium-technetium subtraction scans were performed by using 2 mCi of thallium followed by 2 mCi of pertechnetate (Fig 1). For sestamibi parathyroid scintiscans, 25 mCi of technetium Tc 99m–labelled sestamibi agent was injected intravenously. Images of the neck and thorax were obtained after 10 minutes and 3 hours. Abnormal parathyroid glands had a delayed wash-out rate compared with normal parathyroid tissue; hence, abnormal glands were visible as areas of increased focal uptake that persisted during late imaging (Fig 2).

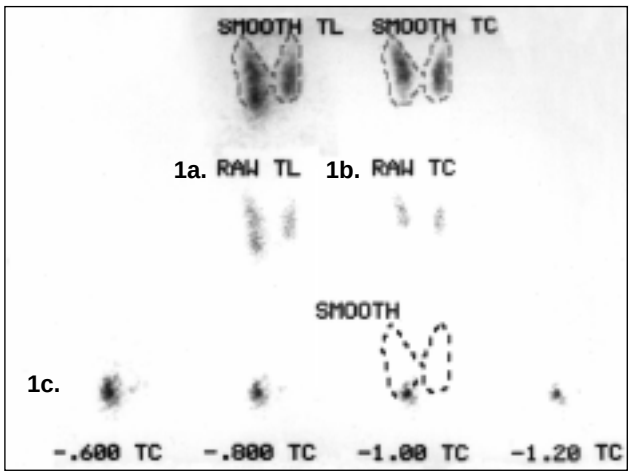

Fig 1. Thallium-technetium subtraction scans of a patient with primary hyperparathyroidism
(1a) thallium uptake by both thyroid glands and an adenoma in the parathyroid gland; (1b) technetium uptake by the thyroid glands only; (1c) subtraction of thallium and technetium scans shows the adenoma in the right inferior parathyroid gland

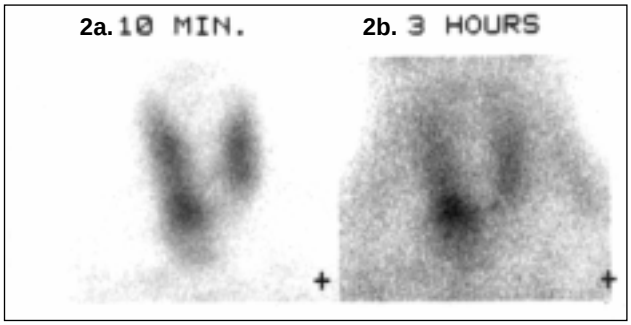

Fig 2. Technetium Tc 99m sestamibi scans of a patient with primary hyperparathyroidism
(2a) early scanning at 10 minutes after intravenous injection of technetium Tc 99m sestamibi shows uptake by both thyroid glands and an adenoma in the parathyroid gland; (2b) late imaging at 3 hours after injection shows a persistently increased focal uptake by the adenoma in the right inferior parathyroid gland

Before each parathyroidectomy, the performing surgeon was informed of the results from the localisation studies. Intra-operatively, the neck was routinely explored to localise all four parathyroid glands. Atrophy of other glands supported the diagnosis of parathyroid adenoma, whereas enlargement of all glands suggested hyperplasia. Adenomectomy was performed for patients with adenoma, and subtotal parathyroidectomy (ie of three and a half glands) was performed for patients with hyperplasia. Diagnoses were confirmed by histological examination. The patients were followed up for any postoperative complications. Comparisons were made between results from the preoperative localisation studies and the intra-operative findings to determine their diagnostic sensitivity, which was defined as the number of true positives divided by the sum of true positives and false negatives. Since 1994, patients have been referred to one surgeon at the QEH.

Results

Clinical characteristics

Forty-four patients were included in the study; there were 13 men and 31 women (male to female ratio, 1:2.4). The mean age was 60 years (range, 21-81 years); 29 (65.91%) of the patients were aged >50 years and two (0.05%) were aged <30 years. Twenty-five (56.8%) patients were asymptomatic. The other patients presented with one or more of the following symptoms: constipation, polyuria, abdominal pain, bone pain, or neuropsychiatric symptoms (Table 1a). Associated complications were diabetes mellitus, hypertension, and the presence of renal stones (Table 1b). Three (6.8%) patients had X-rays with features that were typical of subperiosteal bone resorption or Brown's tumour.

Table 1. Clinical presentation of primary hyperparathyroidism

Presentation	Patients, n=44 No. (%)
1a. Symptoms	
asymptomatic	25 (56.8)
constipation	5 (11.4)
polyuria	8 (18.2)
abdominal pain	7 (15.9)
bone pain	6 (13.6)
neuropsychiatric symptoms	6 (13.6)
1b. Associated diseases	
diabetes mellitus	14 (31.8)
hypertension	23 (52.3)
renal stones	7 (15.9)

All patients had elevated serum calcium levels which ranged from 2.75 to 4.17 mmol/L; the median level was 2.98 mmol/L (normal range, 2.20-2.58 mmol/L). The mean calcium level of asymptomatic patients, however, was not statistically different from that of symptomatic patients. Thirty-eight (86.4%) of the patients had clearly elevated PTH concentrations. The remaining six (13.6%) patients had PTH concentrations at the upper limit of the normal range (normal range, 10-65 pg/mL), which were inappropriately high in association with hypercalcaemia. The mean serum phosphate level was at the lower limit of the normal range, at 0.7 mmol/L (normal range, 0.7-1.0 mmol/L); 16 (36.4%) patients had phosphate levels of <0.7 mmol/L. The serum alkaline phosphatase levels ranged from 69 to 1021 U/L and the median was 119 U/L (normal range, 30-120 U/L); 20 (45.5%) patients had elevated alkaline phosphatase activity. Serum creatinine levels were elevated to >120 μmol/L in 10 (22.7%) patients (normal range, 50-110 μmol/L). The mean urinary calcium excretion rate was 6.6 mmol/d (normal range, 3.5-7.5 mmol/d). Eighteen (40.9%) patients were hypercalciuric and had calcium excretion rates of >7.5 mmol/d. Five patients had excessive urinary calcium excretion (>10 mmol/d) which, in the United States, is an indication for parathyroid surgery.

Localisation studies

The number and type of localisation studies performed for our series of patients varied during the study period. Of the 37 patients who underwent parathyroidectomy, a total of 23 CT scans, 25 ultrasonograms, 28 Th-Tc scans, and 14 sestamibi scans were performed. Technetium Tc 99m sestamibi scans were first used at the QEH in January 1995; thus, significantly fewer sestamibi scans were performed. The sensitivities of CT, ultrasonography, Th-Tc subtraction scanning, and sestamibi scanning to detect parathyroid adenomas were 30.4%, 36.0%, 53.6%, and 64.3%, respectively. Conventional CT was performed for 18 patients; spiral CT was performed for 5 patients. Our data did not show superiority of spiral CT over conventional CT, despite the small sample size.

Results that compare the methods of functional localisation in pairs are shown in Table 2. Eight patients had both sestamibi and Th-Tc subtraction scans performed (Table 2a). Both scans gave negative results for four patients; however, sestamibi scans enabled the localisation of two adenomas that could not be imaged using the subtraction scans. In contrast, Th-Tc subtraction scans did not enable the localisation of any parathyroid adenoma that was not detected using a sestamibi scan.

Fourteen patients underwent anatomical examination of the neck using CT and ultrasonography (Table 2b). Both tests gave negative results for seven patients. In two patients, CT detected an adenoma that was missed using ultrasonography; the reverse occurred for three patients. Both ultrasonography and sestamibi scans were performed for nine patients (Table 2c). Adenomas in three patients could not be localised by either method. The use of sestamibi scans enabled the localisation of four adenomas that were not detected using ultrasonography.

Both CT and sestamibi scans were performed for six patients (Table 2d). Both tests gave negative results in three patients. In three other patients, sestamibi scans

Table 2. Comparison of localisation methods

Pair of methods		No. of cases	
2a.	Sestamibi and Th-Tc* subtraction scanning		
		Th-Tc +ve	Th-Tc –ve
	sestamibi +ve	2	2
	sestamibi –ve	0	4
2b.	CT† and USG‡		
		USG +ve	USG –ve
	CT +ve	2	2
	CT –ve	3	7
2c.	Sestamibi scanning and USG		
		USG +ve	USG –ve
	Sestamibi +ve	2	4
	Sestamibi –ve	0	3
2d.	Sestamibi scanning and CT		
		CT +ve	CT –ve
	Sestamibi +ve	0	3
	Sestamibi –ve	0	3

*Th-Tc Thallium-technetium
†CT Computed tomography
‡USG Ultrasonography

detected an adenoma that was missed using CT. Before the introduction of sestamibi scanning in 1995, preoperative localisation had failed in 7 (35.0%) of 20 patients. Between 1995 and 1996, adenoma localisation failed in 5 (29.4%) of 17 patients; 2 of the 5 patients had parathyroid hyperplasia.

Surgical outcome

Thirty-four (91.9%) of the patients had primary hyperparathyroidism due to adenoma in one parathyroid gland. The location and number of adenomas are shown in the Box. Two (5.3%) patients had parathyroid hyperplasia and one patient died of parathyroid carcinoma. Nineteen (43.2%) patients were medically treated preoperatively to reduce their serum calcium levels. Fifteen (34.1%) patients were given oral phosphate and nine (20.5%) were given intermittent doses of intravenous pamidronate; five patients received both drugs. The mean reduction in serum calcium level during treatment with oral phosphate was 0.16 mmol/L, compared with 0.36 mmol/L for patients who had received intravenous infusions of pamidronate.

After exclusion of the patient with parathyroid carcinoma, the postoperative cure rate was 94.4%. There were two cases of surgical failure, as defined by the postoperative persistence or recurrence of hypercalcaemia. One patient had recurrent hypercalcaemia after excision of the right inferior parathyroid gland. Upon re-operation, an adenoma of the right superior parathyroid gland was successfully removed. The second patient, whose preoperative localisation tests had failed, had an adenoma of the left inferior parathyroid gland removed. The serum calcium concentration subsequently decreased from 2.95 to 2.65 mmol/L. Only three parathyroid glands were found during the operation, however, and the right superior parathyroid gland could not be identified. The patient remained hypercalcaemic despite the decline in the serum calcium level. Postoperative scans had remained negative for 3 years after the operation, and the patient was asymptomatic, which is suggestive of multiple adenomata or parathyroid hyperplasia.

Location of parathyroid gland adenomas

Location	No. of adenomas
Right superior gland	11
Right inferior gland	9
Left superior gland	4
Left inferior gland	8
Intrathyroidal	1
Behind manubrium	1

Postoperative hypocalcaemia developed in 11 (29.7%) patients. The mean nadir postoperative calcium level was 1.82 mmol/L. Hypocalcaemia usually developed within 24 to 48 hours postoperatively. In eight of the patients, hypocalcaemia was transient and there was spontaneous recovery in 12 to 20 weeks. Three patients developed permanent hypocalcaemia and required long-term treatment with 1,25-dihydroxycholecalciferol and calcium supplementation. There were no patients with recurrent laryngeal nerve palsy.

Discussion

Primary hyperparathyroidism and humoral hypercalcaemia of malignancy account for approximately 90% of all cases of hypercalcaemia.[3] In the general population, primary hyperparathyroidism is more common than malignancy. The prevalence of the former since the widespread use of multichannel serum chemistry auto-analysers is approximately 0.1% in the United States.[4] It affects predominantly postmenopausal women and its peak incidence is in the fifth to sixth decades of life. The ratio of affected males to females is 1:3.[3] Our data show similar patterns of sex and age distribution. Up to 66% of patients were older than 50 years and the male to female ratio was 1:2.4.

Patients with hyperparathyroidism classically present with urinary, bone, and gastrointestinal symptoms, commonly known in the medical profession as 'stones, bones, and abdominal groans'.[3] Among 343 patients with primary hyperparathyroidism who were treated at the Massachusetts General Hospital in the 1960s, more than 50% of patients had urolithiasis. Nearly 25% of patients had classic parathyroid bone disease, as characterised by subperiosteal bone resorption, osteitis fibrosa cystica, salt-and-pepper appearance of the skull, and brown tumours. Only 0.6% of patients were asymptomatic.[5] In contrast, with the advent of multichannel auto-analysers, up to 80% of patients with primary hyperparathyroidism in a recent series were asymptomatic at diagnosis.[1] There was also a significant reduction in the frequency of radiologically apparent cases of bone disease (frequency, 1% - 2%).[1] In our series, more than half of the patients were asymptomatic, and 6.8% showed X-ray changes that indicated parathyroid bone disease. Early detection may probably explain the low incidence of radiologically apparent cases of bone disease among our patients; increased vitamin D intake may have also contributed. The use of X-rays, however, is not sensitive in detecting parathyroid bone disease,[3] and we are now using dual energy X-ray absorptiometry to determine bone involvement. The frequency of nephrolithiasis in

our series of patients (15% - 20%) was similar to that in the series described by Bilezikian et al.[1]

The diagnostic hallmarks of primary hyperparathyroidism are hypercalcaemia and elevated PTH levels. Measurement of intact PTH by two-site immunoradiometric or immunochemiluminometric assays is preferable.[6] Assays which measure C-terminal PTH alone can give falsely elevated levels when renal excretion is impaired. In the series described by Nussbaum and Potts,[6] more than 90% of patients with primary hyperparathyroidism had elevated levels of circulating intact PTH. In our series, 86.4% of patients had elevated PTH levels. The remaining patients had PTH levels that were at the upper limit of the normal range, and abnormally high for cases of elevated serum calcium. The PTH concentration is suppressed in virtually all other causes of hypercalcaemia, including humoral hypercalcaemia of malignancy.[3] Rare exceptions include lithium- and thiazide-associated hypercalcaemia, familial hypocalciuric hypercalcaemia, and a few cases of ectopic production of authentic PTH.[7-9]

Approximately one third of our series of patients had low serum phosphate levels. Alkaline phosphatase activity was elevated in 20 (45.5%) of the patients and reflected the increased bone turnover. In addition, 18 (40.9%) patients had elevated rates of urinary calcium excretion and were therefore at risk for the development of renal stones.

Various techniques have been used for the preoperative localisation of hyperfunctioning parathyroid tissue. The most commonly used are Th-Tc subtraction scans, ultrasonography, and CT. Reported sensitivities vary widely: from 27% to 68% for Th-Tc subtraction scanning,[10,11] 36% to 76% for high resolution ultrasonography,[11,12] and 46% to 55% for CT.[11] The high variation in sensitivity from centre to centre may reflect the availability of local expertise. In our centre, conventional CT was the least sensitive method of localisation. Spiral CT may have a higher sensitivity and was introduced to our centre only after 1994; thus, our experience with it is still limited.

Initially developed as a myocardial perfusing agent, sestamibi was demonstrated by Coakley et al in 1989 to be a potential parathyroid imaging agent.[13] Because sestamibi is sequestered in mitochondria, the large number of mitochondria found in parathyroid adenomas have been suggested to be the basis for the delayed release of sestamibi from the parathyroid tissue.[14] Radioisotope scintiscans depend on the metabolism of the radioisotopic agent by the hyperfunctioning parathyroid tissue and thus allow functional localisation, whereas ultrasonography and CT provide anatomical localisation. This study shows that functional scintiscans were superior in sensitivity (50% - 65%) when compared with anatomical scans (30% - 36%). In addition, sestamibi scans were more sensitive (64.3%) than Th-Tc subtraction scans (53.6%). Other groups have reported an even higher sensitivity for sestamibi scanning (up to 85%), especially when used in conjunction with single photon emission CT.[15,16] In general, lower sensitivities were reported for patients with parathyroid hyperplasia.[17] Up to 10 adenomas that could not be localised by any radiological imaging methods were successfully removed during parathyroid explorations. This success lends support to the notion that preoperative localisation is not necessary for a patient who has not previously undergone any neck surgery. To quote Doppman and Miller: "The best localisation technique is to locate an experienced parathyroid surgeon".[18]

Surgery is the only definitive therapy for primary hyperparathyroidism. Removal of the adenomatous or hyperplastic tissue corrects the hypercalcaemia and normalises the PTH level. Our surgical cure efficiency of primary hyperparathyroidism was 94.4%, which is comparable to reported results of other experienced parathyroid surgeons.[19,20] Surgical expertise is important, as surgical failure is either due to technical inexperience of surgeons or the presence of supernumerary, ectopic, or multiple abnormal glands.[21,22] The availability of an experienced parathyroid surgeon at the QEH and the higher sensitivity of functional imaging studies have allowed us to modify our practice to using either no or only one (ie sestamibi scanning) preoperative localisation study in patients who have not had neck surgery. A sestamibi scan is performed for patients with high surgical risk, in an attempt to shorten the operative time.

Our frequency of postoperative hypocalcaemia was 20% to 40%, which was similar to that reported in another series.[23] In this study, most cases of hypocalcaemia were transient and possibly due to short-term suppression of other parathyroid glands by the hyperfunctioning adenoma, or due to 'hungry bone' syndrome. Permanent hypocalcaemia developed in three patients.

At the Consensus Development Conference on the 'Diagnosis and management of asymptomatic primary hyperparathyroidism' that was held in 1991, a set of surgical guidelines was endorsed.[24] Suggested indications for operation included a serum calcium concentration of >2.99 mmol/L, marked hypercalciuria

with a urinary calcium excretion rate of >10 mmol/d, the presence of any overt complication of primary hyperparathyroidism (eg nephrolithiasis, osteitis fibrosa cystica, or classic neuromuscular disease), a reduced creatinine clearance in the absence of other causes, a reduction in bone density of more than two standard deviations below normal at the site of the cortical bone, an episode of acute primary hyperparathyroidism, and an age of <50 years. Taking into consideration the availability of surgical expertise and the high cure rate in our centre, we tend to favour surgery if the medical condition of the patient permits. In our series, 90% of patients underwent parathyroidectomy.

Patients who did not undergo parathyroidectomy were managed by adequate fluid intake, avoidance of thiazide diuretics, and immobilisation. Dietary calcium was not restricted, although we advised against an excessively high intake. The natural course of the disease in these patients has not been analysed in this study, which mainly included patients who had had pathological confirmation of resected parathyroids. Others[25] reported a rather benign course in the majority of patients with mild disease, stable calcium and PTH levels, and biochemical markers of bone turnover for up to 6 years. Annual bone mass measurements did not demonstrate any significant changes at any site.[25] These observations, however, do not obviate the need for life-long follow-up. Whether patients who have more severe disease would experience a similarly benign course is not certain.

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