Bone and Renal Stone Disease in Patients Operated for Primary Hyperparathyroidism in Pakistan: Is the Pattern of Disease different from the West?

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Abstract

Objective: To document the clinical presentation of primary hyperparathyroidism (PHPT) in a developing country and note differences from the West.
Setting: A tertiary care teaching hospital.
Method: The records of 37 patients operated for PHPT between January 1986 and December 1997 were reviewed. Symptoms, laboratory parameters and histopathology results were analyzed.
Results: Surgery for PHPT accounted for 0.055% of 67,566 operative procedures performed in the Department of Surgery during the 12 year period. The mean age of our patients was 38.4±13.2 years (range 17 to 73 years). Ninety percent of patients were less than 60 years old and 51% less than 40 years.
At presentation, the mean serum parathyroid hormone (sPTH) level was 618±741% abvoe the upper limit of normal (range 0-2900% using a variety of assays). A solitary adenoma was present in 86.5%, hyperplasia in 5.4% and carcinoma in 5.4% of patients. There was one (2.7%) negative exploration. Thirty-five percent of patients had renal stone disease (StD), 32.4% had bone disease alone (BD) and 27% had both bone abnormality and stones (BStD). There were neither bone disease nor stones in 5.4% of patients.
BD was associated with a statistically non-significantly (p=O.O8) higher alkaline phosphatase level (sALP) as compared to the StD and BStD groups. The mean urinary calcium (Ca) was higher in the BD group (482±340 mg/24 hours) as compared to StD group (265±89 mg/24 hours) (pO.Ol3). The post-operative hospital stay was longer in the BD group (14.4±16 days) as compared to the StD group (6.7±3.7 days) (p=0.001).
Conclusion: As compared to reports from the Western world, PHPT is less commonly diagnosed in our country and occurs at a younger age. In the absence of a screening programme, symptomatic disease and bone involvement occur more frequently. The high levels of PTH may indicate long-standing disease in our population, which may account for higher proportion of patients with symptoms. Unexpectedly. patients with bone disease had higher levels of urinary calcium than patients with stone disease (JPM A 49:194, 1999).

Introduction

A diagnosis of primary hyperparathyroidism (PHPT) is rarely made in Pakistan. This may. result from lack of awareness and lack of screening. We screen all stone patients by determining the serum calcium level and have reported PIIPT in 1.25%[1]. We do not routinely screen postmenopausal women at our hospital and this is generally not done in Pakistan. Over a period of 12 years, we have operated on 37 patients with PHPT. Some were detected through screening and others presenting with bone pain, were referred by orthopedic surgeons. We retrospectively reviewed the clinical and histological features in order to define the pattern of the disease in Pakistan.

Patients and Methods

The case records of 37 patients who underwent parathyroidectomy between January 1986 and December 1997 were reviewed. The number of operations done in the Department of Surgery for the corresponding period was obtained from the coding department. These included urological, general surgical, vascular, neurosurgical and orthopedic procedures but excluded obstetrical and gynecological procedures. Data was recorded on age, sex, presenting symptoms, preoperative serum biochemistry, 24 hours urinary calcium (Ca) excretion, location and histopathology of the glands and post-operative hospital stay. Serum biochemistry included serum Ca, Phosphorus (P), Parathyroid hormone (PTH), alkaline phosphatase (sALP) and magnesium (Mg).

Initially. PTH levels were estimated by radioimrnunoassay using middle molecule. In the later part of the study, intact parathyroid hormone (iPTH) was measured. In order to compare PTH results determined by different assays, in which the normal ranges of the PTH were different, PTH levels were expressed as percent measure above the upper limit of normal by the following formula: % PTH increase= limit of normal)/upper limit of normal] x100.

Patients were classified as those with bone disease (BD), stone disease (StD) or with both (BStD). BD was defined as the presence of persistent bone pain, pathological fractures or other radiological evidence of bone disease, such as subperiosteal erosions, bone cysts or evidence of bone resorption on conventional X-rays. Microradiographs (magnified view of the hand) performed on mammography film and dual photon absorptiometry were used infrequently. Patients were classified as having stone disease if there was a past history of urolithiasis, demonstrable stones in the urinary tract or nephrocalcinosis.

Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS)R for Windows version 6.0 Student's t test was used for comparisons. Linear regression was used to assess the relationship of variables. $P<0.05$ was considered as statistically significant.

Results

A total of 37 patients underwent parathyroidectomy. Surgery for PHPT was performed in 0.055% of the 67,566 surgical procedures. The mean age of our patients was 38.4±.13.2 years (range 17 to 73 yeats). Ninety percent of patients were <60 years old, 70% <45 years old and 51% <40 years. Two patients were below 20 years of age. Females out-numbered males (2.4:1). The age and sex distribution is depicted in Figure 1.

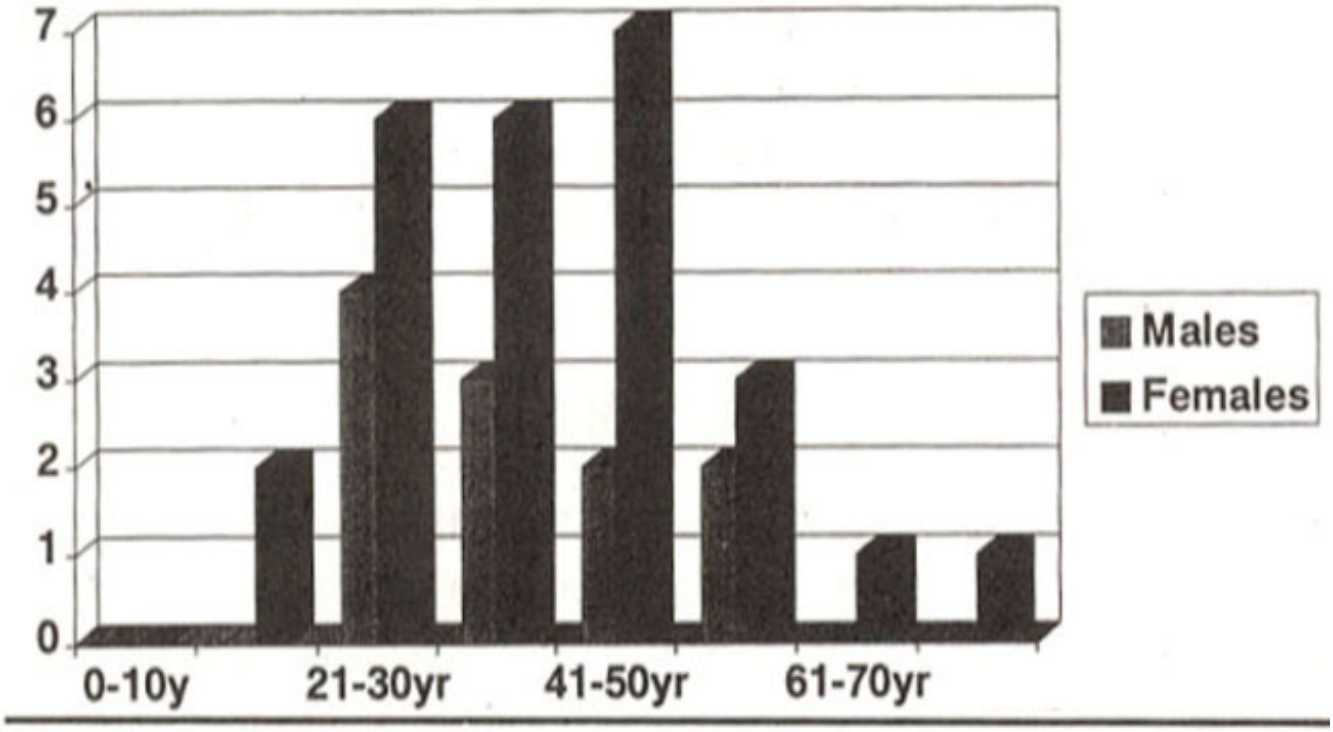

Figure 1. Age and sex distribution.

At presentation, 12 patients had bone disease, 11 had stone disease, 10 had both bone and stone disease. One each presented with asymptom atic hypercalcern ia, recurrent peptic ulcer and hypercalcemic crisis. One patient was asymptomatic and had a thyroid lobectomy for multinodular goitre and was found to have a parathyroid adenoma post operatively (Figure 2).

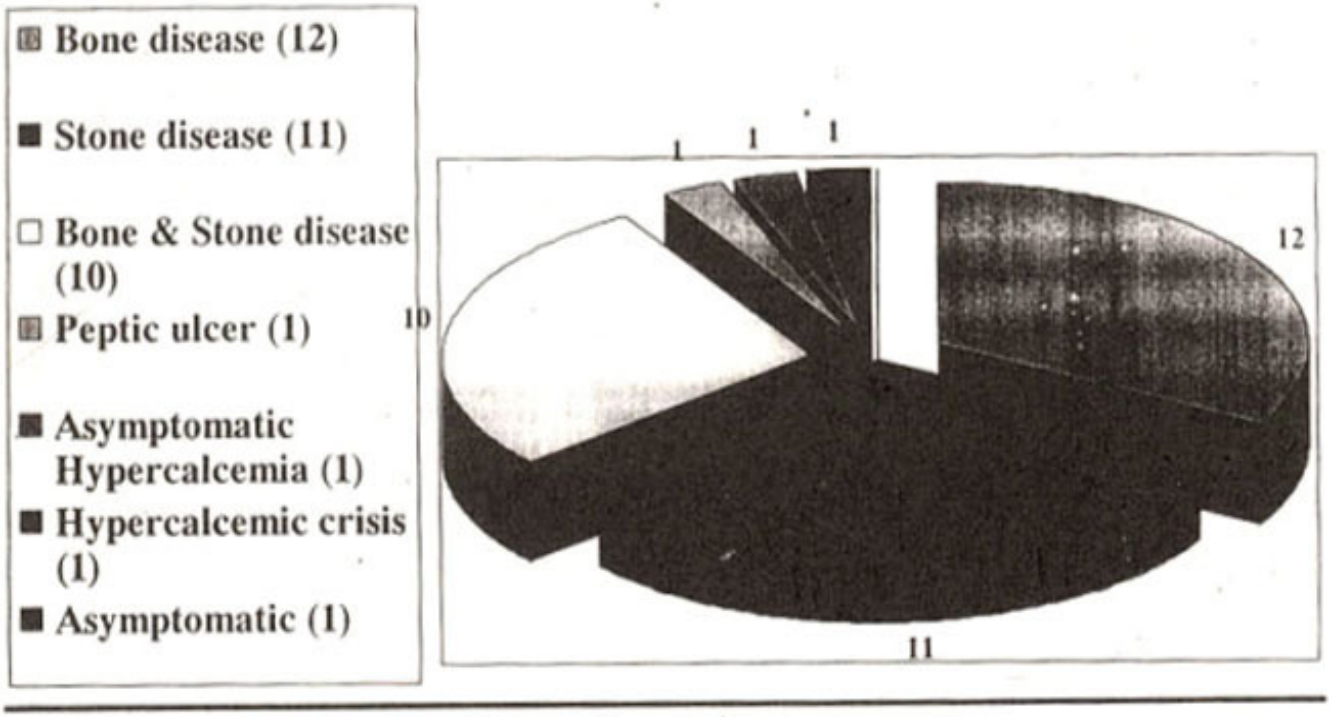

Figure 2. Presentation.

After investigation StD was detected in an additional 2 patients (StD=13) (35.1%). BD was found in 12

(32.4%) and BStD in 10 (27%) patients. Two patients (5.5%) had neither bone nor stone disease.
The mean pre-operative serum Ca level in 36 patients was 12.2±1.8 mg/dl (normal range: 8.6 to 10.5 mg/dl).The mean serum Phosphorus (P) was 2.32±0.80 mg/dl (n=35, normal range=2.4 to 4.8 rng/dl), serum Mg was 1.86±0.38 mg/dl (normal:1.9-2.5). Serum Alkaline Phosphatase (sALP) was 556±11.39 U/L (29-132) and 24 hour urinary Ca was 375 mg./24 hours (100-300).
The mean serum PTH (sPTH) level was 618±741% above the upper limit of the respective normal value as given by the applied method (range of 0 to 2900%) (Table 1).

Table 1. Serum and urinary values in patients with primary hyperparathyroidism.

Parameter estimated	Normal range	Value (mean±SD)
Serum PTH (% above upper limit)*		681±741%
Serum Ca	8.6-10.5 mg/dl	12.2+1.8
Serum P	2.7-4.8 mg/dl	2.32±0.80
Serum Mg	1.9-2.5 mg/dl	1.86±0.38
Serum ALP	29-32 IU/L	557±1139
Urinary Ca	100-300 mg/24 hours	375±223

*Value calculated for comparison (explained in the text).

In one patient the sPTH was just within the upper limit of normal. This patient had a serum calcium of 12 mg/dl and the serum PTH was inappropriately suggesting PHPT. This patient had an arteriogram which localized an adenoma.
There was no significant difference in serum Ca, P and Mg between the BD and StD group (Table 2) sALP was higher in the BD group as compared to the StD group (p=0.08) (Figure 3).

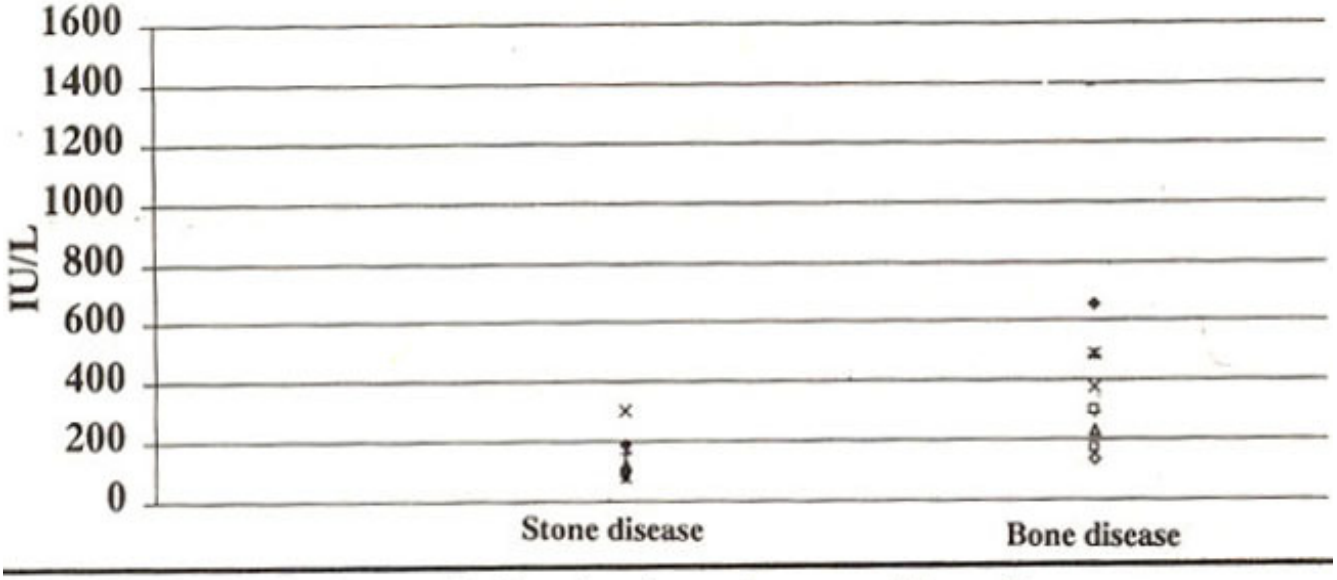

Figure 3. Serum alkaline phosphatase in stone and bone disease.

The urinary Ca was higher in the BD group (0.013) (Figure 4).

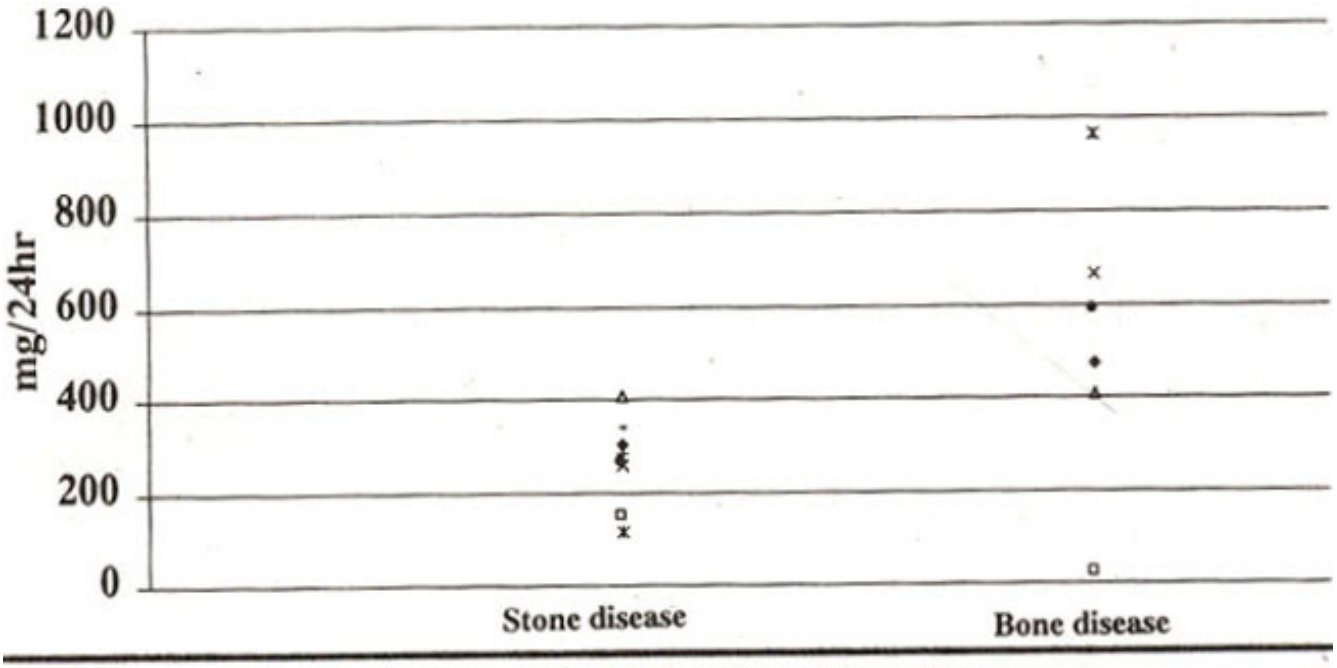

Figure 4. Urinary calcium in stone and bone disease.

Bone disease necessiatated a longer post operative stay (14.4±16 days) as compared to StD (6.7±3.3 days) (p=0.001) (Table 2).

Table 2. Difference between stone and bone disease patients*.

	Bone disease (BD)	Stone disease (BStD)	p value
Serum PTH (% above upper limit)	830±933	495±675	0.2
Serum calcium (mg/dl) (8.6-10.5)	12.5±1.7	11.8±1.6	0.6
Serum phosphorus (mgdl) (2.7-4.8)	2.05±0.13	2.5±0.65	0.49
Serum Magnesium (mg/dl) (1.9-2.5)	1.8±0.13	2.3±0.22	0.42
Serum Alkaline Phosphatase IU/L (29-132)	906±1659	149±72	0.08
Urinary calcium (mg/24 hours) (100-300)	482±340	265±89	0.013
Post operative Stay (days)	14.4±16	6.7±3.3	0.001

*Patients with both bone and stone disease are exlcuded.
All values are mean±SD.

There was no correlation between gland size and sPTH (r=0.07), sPTH and sCa (r=0.09) or sPTH and post operative length of stay (r=O.24).
A median sternotomy was required in two patients. All other patients were operated through the neck. There were two negative explorations. One patient underwent successful re-exploration by median sternotomy after two negative neck explorations. The location of the lesions (excluding hyperplasia) are shown in figure 5.

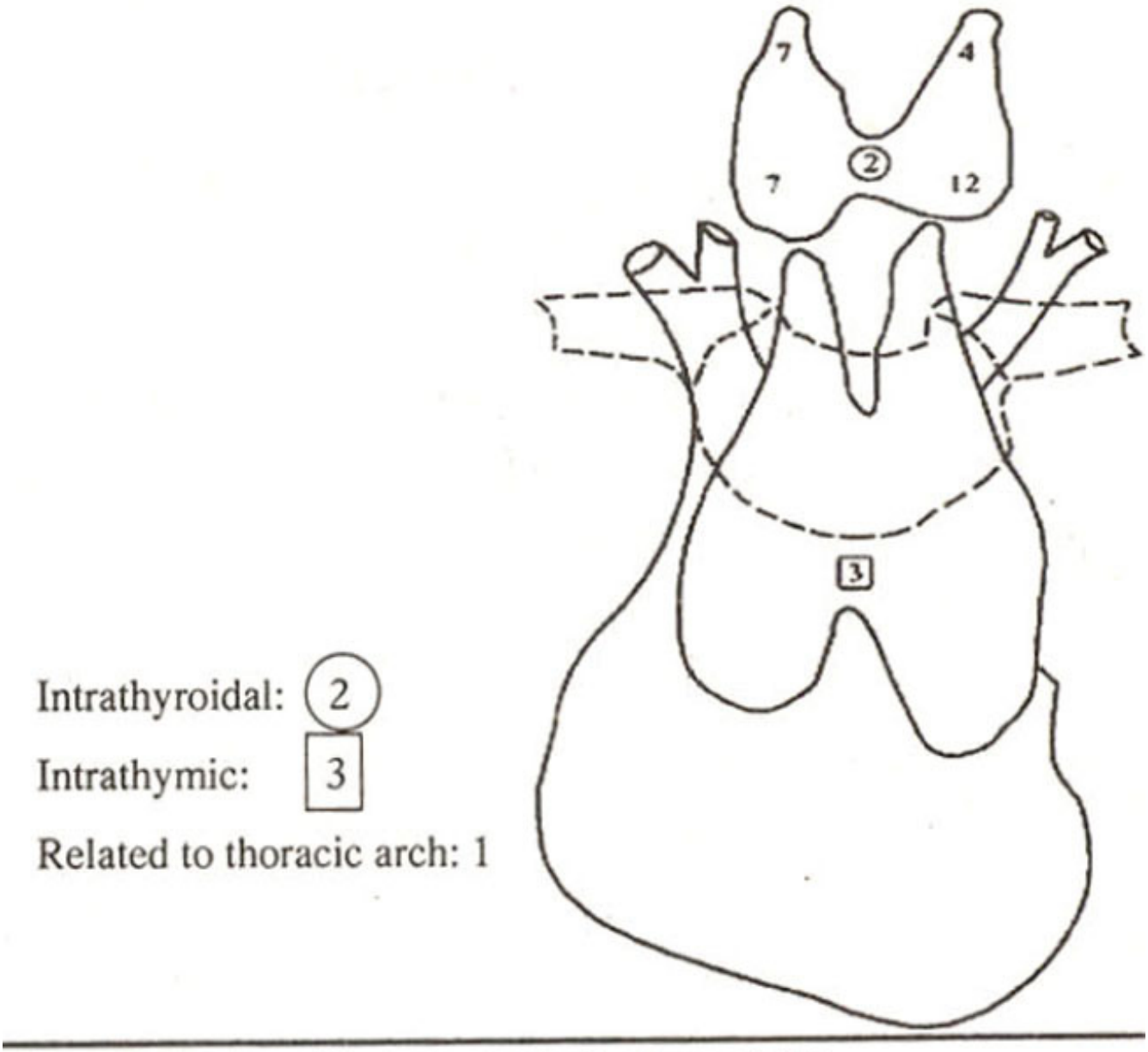

Figure 5. Location of the lesion (excluding hyperplasia).

Four patients had mediastinal adenomas; two had intrathyroidal adenomas. Of the four extra cervical lesions, 2 were removed through standard cervical incisions. Histopathology revealed 32 (86.5%) adenomas, 2 (5.4%) hyperplasias and 2 (5.4%) carcinoma. There was one negative exploration (2.7%).

Discussion

The incidence of PHPT in Pakistan is not known. It has been reported in 1.25% in stone patients[1]. In the West, PHPT an incidence of 188/100,000 in patients above 60 years of age has been reported, compared with 25/100,000 of the general population[2].

Our results suggest that PHPT may be less common here than in the West, where endocrine surgical units perform 72-192 parathyroidectomies per year[3,4]. In the West, PHPT is commonest in post-menopausal women. In our series also we have operated on twice as many women as men. The mean age (38.4±13.3 years) of patients was considerably younger in our population as compared to the West,

where 12% of the patients are younger than 45 years of age[5]. In contrast, 70% of our patients were in that age group.

PHPT in Pakistan is rarely detected in an asymptomatic stage. In our series, only 2 patients (5.4%) had mild or no symptoms where as 34 (91.9%) presented with either bone or stone disease and one with a hypercalcemic crisis. Many presented with severe changes in bones as a result of long standing disease. This is most likely due to a lack of awareness and of diagnostic screening in our country and parallels earlier reports from the West (1961-1 979) [6,7].

Stone disease was present in 62% of our patients. This is similar to earlier studies from the West[8]. However, in the West, due to screening programs, early detection of the disease is now the rule. Patients presenting with symptomatic stone or bone disease now account for less than 10% of cases there[5,6,9]. In the West, PHPT is now a cause of stone disease in as few as 0.17%[10] as compared to 125% in Pakistan[1].

A positive correlation has been reported between parathyroid gland weight, serum Ca and PTH concentrations in PHPT[11]. In contrast, there was no correlation in our study between gland size and Serum Ca (r=0.03) and PTH (r=0.07). Likewise, there was no correlation between duration of hospital stay and PTH (r=0.24) or sALP and PTH (r0. 14).

Unexpectedly, there was a high mean urinary Ca excretion in BD group. Hypercalciuria in bone disease, as seen in our patients, most likely reflects bone destruction in advanced disease such as is frequently present in our patients. Generally, stone disease patients have been described to have higher urinary Ca excretion which has been explained on the basis of a higher renal mass and vitamin D reserve and hence higher intestinal absorption of calcium, seen especially in younger patients[12].

There was a higher incidence of BD than in the West. However, it has to be borne in mind that recent detailed studies with photon absorptiometry have somewhat blurred the distinction between SD and BD[6,13]. In one study, bone mineral density was reported to be the same in stone and bone patients, suggesting that PHPT can no longer be divided into bone or stone disease[7]. In our patients, sALP clearly demarcates patients with severe bone disease. This is also reflected in the post operative course. Patients with hungry bones (those with severe metabolic bone disease) and increased alkaline phosphatase levels require longer and more intense calcium replacement and consequently, a longer hospital stay. Braiser has indicated the different post operative behavior (longer hospital stay) in patients with hungry bone disease[3]. The serum alkaline phosphatase seems to be a good predictor of post operative hospital stay and hungry bone syndrome.

In conclusion, there are differences in the pattern of disease between this series and contemporary series from the West. PHPT is less frequently detected in our population and its prevalence may be low. It presents in a younger population and in an advanced and nearly always symptomatic stage with severe disease. Severe bone disease is still frequently seen and these patients have a high urinary Ca level suggesting an aggressive and/or prolonged course of disease. The post operative hospital stay is longer in bone disease patients. There is a high proportion of patients with stone disease secondary to PHPT. Serum Ca or sPTH are not significantly related to gland size.

Acknowledgments

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