Original Article

Clinical Presentation and Outcome of Surgical Management of Primary Hyperparathyroidism: A Single Center-based Case Series in Egypt

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ABSTRACT

Introduction: Primary hyperparathyroidism is an asymptomatic disease in the Western world detected during routine laboratory investigations.The differential diagnosis and the management of primary hyperparathyroidism presenting with more severe symptoms like Skeletal manifestations present a challenge to the surgeon from similar presenting conditions like bone metastases and bone tumors. **Objectives:** To describe the presentation and the management of primary hyperparathyroidism in the context of limited resources and the challenges faced with the differential diagnosis, especially with the dominance of the skeletal manifestations of the disease. **Patients and Methods:** Patients presenting with primary hyperparathyroidism during the period from 2010 to 2014 in the National Cancer Institute in Egypt were included in the study. Data were retrieved retrospectively from the files (demographic, pathological, preoperative investigations, surgical approaches, and outcome). **Results:** In this study, 23 patients were included with an age range of 12–69 years, skeletal manifestations predominated the presentation of the primary hyperparathyroidism in 66.6%, and unilateral neck exploration was the main surgical approach done in 70.8%. The 1-year overall survival is 100% and 1-year relapse-free survival is 92.9%; 17 cases (73.92%) were cured and 6 cases (26.08%) had persistent hyperparathyroidism. **Conclusion:** The skeletal manifestations predominates primary hyperparathyroidism presentation in this study. The clinician should be aware of the bony manifestations mimicking bone tumors and metastatic tumors to the bone. Calcium and parathyroid hormone levels should be done first before attempting excision of the tumor, especially if it involves the maxilla or mandible. Surgery is curative for symptomatic cases in different age groups with low incidence of complications, recurrence, and persistence of the disease.

Key words: Clinical presentation, outcome, primary hyperparathyroidism, skeletal manifestations, surgical approach

INTRODUCTION

Primary hyperparathyroidism represents the 3rd most common endocrine pathology.[1] The most common presentation in the Western world is asymptomatic hypercalcemia detected during routine laboratory investigation.[2] In many areas of the world like India[3] and Iran,[4] the disease is still presenting in its severe form of skeletal manifestations, abdominal groans, and psychic moans as it was originally described historically by Catchpole in 1949.[5]

Primary hyperparathyroidism is a rare disease with an incidence of 21 cases per 100,000 population/year.

In this study, we delineate the main characteristics of our patients presenting to a tertiary cancer care center in Egypt with a presentation mimicking bone metastasis and bony tumors in some cases. The clinical and pathological presentation with special focus on the differences between different countries, age, and gender as well as the diagnostic challenges is underlined.

The management of symptomatic primary hyperparathyroidism including preoperative localization techniques and surgical approaches varies according to availability of resources among the world, especially in developing countries with limited resources. The limitations of intraoperative localization of the parathyroid glands and the outcome of the surgical treatment of our patients will also be discussed.

We have studied primary hyperparathyroidism in a population in Egypt presenting to a tertiary cancer center in four consecutive years and found similar clinical presentation to developing countries. The most common presentation is that of bone manifestations.

The presentation itself represents a diagnostic challenge, especially when the only manifestation of the disease is a pathological fracture or multiple bony tumors mimicking metastatic or bone disease.

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In some cases, the patient presents with maxillofacial tumors, and the hyperparathyroidism is diagnosed only postoperatively after maxillectomy or even mandibulectomy.

PATIENTS AND METHODS

This study was conducted at the National Cancer Institute in Cairo from 2010 to 2014, and a total of 23 patients with primary hyperparathyroidism were studied for their clinical presentations, management, surgical approach, and outcome.

All the patients with a final pathological diagnosis of adenoma or hyperplasia of the parathyroid glands were included in the study. Patients with secondary hyperparathyroidism were excluded from the study.

Data retrieved from the files included patient's age, gender, clinical presentation (asymptomatic or symptomatic), and laboratory investigations (pre- and post-operative calcium and parathyroid hormone [PTH] levels).

Asymptomatic primary hyperparathyroidism is defined as hypercalcemia in an otherwise asymptomatic patient detected incidentally on laboratory investigations.[6]

Patients were diagnosed as having primary hyperparathyroidism after thorough investigations and documented preoperative elevation of calcium level as well as PTH.

In few patients, especially those presenting with maxillary, mandibular tumors or pathological fracture, the diagnosis was made postoperatively after an excision of the tumor was done.

Preoperative imaging studies were done (computed tomography [CT], myocardial perfusion [MIBI] scan, and limb X-rays), and the prediction of the preoperative imaging in localizing the tumor was also evaluated.

The surgical approach to the parathyroid glands as well as the number of the glands removed during surgery were reviewed. The final pathology of the removed glands wether adenoma or hyperplasia. The follow up period was reported in months for each case and the status at last follow up was recorded and retrieved from the files.

Outcome was evaluated by assessment of the postoperative status: persistent hyperparathyroidism, recurrent or cured, and the overall survival. Persistent hyperparathyroidism is defined as persistent elevation of PTH <6 months after surgery.[7] Recurrence is defined as elevation of PTH >6 months after curative surgery.[7] The outcome is also discussed in the context of limited resources that prevent the use of advanced techniques in localization and surgery in a tertiary care center in Egypt.

Statistical methodology

Descriptive statistics for enrolled participants are presented as counts and percentages for categorical variables and means and standard deviations for quantitative variables. Statistical associations between presentation type and patients' characteristics were evaluated by independent *t*-test and Chi-square test or Fisher's exact test for quantitative and categorical variables, respectively.

The association between type of surgery and postoperative hyperthyroidism status was evaluated by Fisher's exact test to give a significance level of 0.05. The MIBI scan's ability to differentiate adenomas from hyperplasia was tested by calculating its sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Moreover, survival analysis was conducted by Kaplan–Meier curves to obtain the overall survival and event-free survival (duration from first presentation to relapse date or date of last contact of the patients).

We were waived from the Ethics Committee approval due to the nature of the retrospective study.

RESULTS

Sex and age distribution

Mean age is 40 years (range: 12–69 years) with female predominance (n = 19) (79%) and male representing (21%) (n = 5).

Clinical presentation

Skeletal manifestations constituted the main presentation in 66.6% (n = 17) while only 29.4% had nonskeletal presentations. Skeletal manifestations were present in 88.9% of females and 80% of males. The presentation type is not significantly related to gender (P = 1000). Patients' demographic clinicopathological characteristics are presented in Table 1.

Pathological fractures occurred in the upper humerus, tibia, and pubic ramus in 3 cases (13%), while generalized bony pain was present in seven cases (30.5%), recurrent maxillary swelling in two cases (8.6%) and mandibular swelling in one case (4.34%), neck swelling and thyroiditis in one case (4.34%), bilateral rib swelling in one case (4.34%), back pain in four cases (17.3%), and loin pain in two cases (8.6%), pathologically proven brown tumors after excision of two metaphyseal swellings in the tibia for suspicion of primary bone tumors.

There was no relationship between the size of the adenoma or the number of the glands affected and the severity or type of the presentation.

Laboratory investigations

The diagnosis of primary hyperparathyroidism relied on the PTH level as well as the calcium level elevation. Calcium levels both pre- and post-operative levels are shown in Table 2.

The degree of elevation of the PTH and the calcium level did not showed any statistical significance in correlation with the type of pathology adenoma versus hyperplasia and the severity and type of the symptom presentation of the patient.

PTH level was elevated preoperatively with a mean of 788.7, mean postoperative PTH level was 147.3, and mean decrease in PTH level postoperatively was 680.4.

Table 1: Demographic and clinicopathological characteristics

	Mean±SD or *n* (%)
Age	40.75±18.01
Sex	
Female	19 (79.2)
Male	5 (20.8)
Residency	
Alex	1 (6.7)
Cairo	2 (13.3)
Giza	7 (46.7)
Kalyoubia	2 (13.3)
Menoufiya	1 (6.7)
Menya	1 (6.7)
Sharquiya	1 (6.7)
Presentation type	
Bony	16 (69.6)
Nonbony	7 (30.4)
Laterality	
Bilateral	9 (40.9)
Left	6 (27.3)
Right	7 (31.8)
Pathology	
Adenoma	15 (62.5)
Hyperplasia	9 (37.5)

Table 2: Preoperative and postoperative calcium levels

	n (%)
Calcium preoperative	
High <12	4 (22.2)
High >12	5 (27.8)
Normal	17 (50)
Postoperative	
Low	8 (34.8)
Normal	15 (65.2)

Imaging studies

The main imaging studies done are shown in Table 3.

MIBI scan was used to localize the diseased gland in 75% of cases(n = 18) With a sensitivity of 90.9% and a specificity of 100%. PPV and NPV of MIBI scan are 100% and 85.7%, respectively. The presentation of a pathological fracture mandates a limb X-ray.

Surgical management is outlined in Table 4. The main surgical approach was the unilateral neck exploration used in 70.8% while bilateral neck exploration was used in 29.2%; no minimally invasive endoscopic surgery was done.

Pathology: Parathyroid adenoma represented 62.5% of cases, and a single adenoma was present in all cases. Parathyroid gland hyperplasia was present in 37.5% of cases.

There was no significant relationship between presentation and pathology. Fisher's exact test P value was 0.363.

Outcome

The 1-year overall survival is 100% and 1-year relapse-free survival is 92.9%; persistent hyperparathyroidism was present in 6 cases (26.08%) after surgery while 17 cases (73.92%) were cured with a mean. Follow-up

Table 3: Preoperative investigations

	n (%)
CT	3 (12.5)
MRI	3 (12.5)
Bone scan	6 (25.0)
Neck US	10 (41.7)
MIBI scan	18 (75.0)

CT: Computed tomography, MRI: Magnetic resonance imaging, MIBI: Myocardial perfusion

Table 4: Surgical management

	Mean±SD or *n* (%)
Surgical approach	
KOCKER, bilateral neck exploration	7 (29.2)
KOCKER, unilateral neck exploration	17 (70.8)
Type of surgery	
Excision of 1 glands	7 (30.4)
Excision of 4 glands	6 (26.1)
Hemithyroidectomy	1 (4.3)
Excision of 2 glands	9 (39.1)
PTH implantation in the forearm or neck	
No	20 (83.3)
Yes	4 (16.7)
Time to surgery	6.72±9.11
Hospital stay	4.22±2.52

PTH: Parathyroid hormone, SD: Standard deviation

duration was 19.34 months. Median Follow-up duration was 13.32 months. The relationship between the type of surgery done and the postoperative outcome is shown in Table 5.

DISCUSSION

Clinical presentation and patients' characteristics

Primary hyperparathyroidism presents usually in the six or the seventh decade[1] in contrast to the predominance of a younger age group with a mean age of 40 years in this study.

The residence of the patient did not show any specific relation to the type of symptoms, and most of the patients were from Cairo and Giza, representing urban areas. It is to be noted that Vitamin D deficiency was suggested as an etiological cause of primary hyperparathyroidism, but the incidence of Vitamin D deficiency incidence by geographic area in Egypt is not known.

The presentation of primary hyperparathyroidism in the form of a neck swelling is very rare occurring only in one patient presenting with thyroid swelling due to thyroiditis.

Although difference in clinical presentation of hyperparathyroidism between male and female was demonstrated in a previous study Mazeh *et al*.,[8] our results did not show any difference between genders. This may be due to the small number in the case series with female predominance which is typical of primary hyperparathyroidism in the literature.[8]

The presentation of primary hyperparathyroidism in its classic form changed in the West and in the USA nowadays to an asymptomatic form in the past decade due to the adoption of routine biochemical screening for unrelated causes.[9] Unfortunately, we do not adopt the same policy for screening nationally, and this may have contributed to the severe form of presentation with predominant skeletal presentations (66.6%).

The skeletal presentation of hyperparathyroidism in the USA is considered a form of complicated hyperparathyroidism nowadays.[10] There are published data from other countries like Iran and India[3,11] reporting that they have different disease presentations with predominance of skeletal manifestations and renal disease rather than asymptomatic disease.

The bony manifestations are themselves confusing in the context of the differential diagnosis of bone tumors or metastatic cancer to the bone.

The presence of maxillary brown tumors due to primary hyperparathyroidism has been reported to be very rare being more common in the mandible.[12]

Patients presenting with pathological fractures and maxillary or mandibular swelling in this study were subjected to excisional biopsies and even mandibulectomy in one case or maxillectomy (two cases) before proper diagnosis could be done.

Despite the current limitations of the bone scan use for diagnosis of primary hyperparathyroidism due to the early disease presentation, it was used in our series to differentiate the skeletal presentation from metastatic cancer and to reveal the cause of generalized bony pain presentation, especially in the setting of a tertiary cancer care center.

Table 5: Type of surgery and hyperparathyroidism status postoperative

Type of surgery	Hyperparathyroidism status postoperative		Total
	Free	Persistent	
Excision of 1 gland	6	1	7
Excision of 4 glands	5	1	6
Hemithyroidectomy	1	0	1
Excision of 2 glands	5	4	9
Total	17	6	23

Pathological characteristics

Single adenomas were the most common pathologies found in our patients in concordance with the incidence of parathyroid adenomas and hyperplasia reported in the literature to be 85% and 14%, respectively. Primary hyperparathyroidism due to parathyroid carcinoma was not present in any of our cases. Parathyroid carcinoma represents <1% of the overall causes of primary hyperparathyroidism.[13,14]

Primary hyperparathyroidism due to parathyroid hyperplasia can occur in a sporadic form or as a part of multiple endocrine neoplasia type II syndrome. The cases in this study are all sporadic cases with no positive family history; however, no genetic studies were done to confirm this finding.

Primary hyperparathyroidism nowadays is a laboratory diagnosis with mild hypercalcemia (within 1 mg/dL above the upper limit of normal), is usually asymptomatic, and diagnosed incidentally on routine investigations for minor nonspecific complaints. Normocalcemic hyperparathyroidism was present in 22.2% of the studied population and all were symptomatic. In a previous study, 41% of normocalcemic hyperparathyroidism were symptomatizing and progressing to the full picture of primary hyperparathyroidism.[15] Hypercalcemic hyperparathyroidism has been reported to be present in

up to 44% of cases.[2] However, it was the main form of presentation in our cases (77.8%).

Intact mean preoperative parathyroid level reported in published case series in asymptomatic solitary parathyroid adenoma was 165 pg/ml;[16] in contrast to our cases, the mean preoperative intact parathyroid level in symptomatic adenomas was 634 pg/ml; and for four cases, gland hyperplasia was 848 pg/ml.

These high levels can be explained by the more severe symptomatology present, but still, the intact preoperative parathyroid levels are in favor of benign parathyroid pathology as it is less than four times the normal limit.[17] The intact PTH level in parathyroid carcinoma can reach up to ten times the normal level.

There was no significant relationship between presentation severity and pathology type whether adenoma or hyperplasia.

Management of primary hyperparathyroidism

Preoperative investigations such as X-rays on the limbs with pathological fractures and bone scan as well as neck and abdominal ultrasound were the main preoperative investigations done for the patients in addition to preoperative calcium and MIBI scan for diseased gland localization. CT and magnetic resonance imaging were done occasionally as well as open biopsy.

Management of primary hyperparathyroidism has evolved in recent years, with considerable interest in minimally invasive approaches. Successful localization of the diseased gland(s) by nuclear imaging and anatomical studies, along with rapid intraoperative PTH assay, has allowed for focused and minimally invasive surgical approaches. Patients in whom the preoperative localization studies have identified single-gland adenoma or unilateral disease are candidates for such focused approaches instead of the traditional approach of bilateral exploration.

These imaging techniques have also been critical in the successful management of patients with persistent or recurrent disease.

The use of MIBI scan localization preoperatively as well as the bilateral neck exploration approach in cases of hyperplasia (29.9%) and difficult cases resulted in successful removal of the diseased glands and cure in 73.92% of cases. Failure to remove the diseased glands occurred in 26.08% resulting in persistent hyperparathyroidism.

This traditional surgical approach to parathyroid glands with the goal of identifying and visually inspecting all four parathyroid glands has a reported success rate that exceeds 90%–95%.

Removal of the parathyroid glands in case of hyperplasia has resulted in persistent hypocalcemic state in eight cases (34.8%) with long-life dependence on calcium and Vitamin D supplementation. This complication is a nonavoidable complication after four-gland removal; however, parathyroid reimplantation has been used in accidental removal of parathyroid glands in thyroid surgery.

In this study, four patients underwent parathyroid reimplantation in the brachioradialis muscle, but in all cases, there was a failure of this technique to restore the normocalcemic state of the patients.

This study is limited by its small sample size; however, the incidence of primary hyperparathyroidism is reported to be rare. There is a lack of information on asymptomatic primary hyperparathyroidism due to the absence of routine screening of calcium levels in patients presenting with other diseases.

We are not sure if the presenting sample population is a real reflection of a different presentation of primary hyperparathyroidism in the Egyptian population; however, we want to highlight that further studies should be done to find if there is a correlation between Vitamin D deficiency and skeletal manifestations predominance.

Routine evaluation of serum calcium level in patients presenting with other diseases should be done to detect the subgroup of asymptomatic primary hyperparathyroidism and its incidence in our population as well as the best way of management.

Routine screening of calcium and PTH in all patients presenting with bone tumors or pathological fractures should be done, especially if it involves the mandible or maxilla before attempting any open biopsy or resection.

CONCLUSION

The bony and skeletal symptoms dominated in our patients even in normocalcemic patients, the patients' characteristics at presentation did not differ with age and gender. Pathological characteristics of the disease are conformal with the literature.

The clinician should be aware of the bony manifestations of primary hyperparathyroidism mimicking bone tumors and metastatic tumors to the bone. Calcium and PTH levels should be done first before attempting excision of the tumor, especially if it involves the maxilla or mandible. Surgery is

curative for symptomatic cases in different age groups with low incidence of complications, recurrence, and persistence of the disease.

The use of the classic bilateral neck exploration is a successful technique in the face of limited resources that prevents the use of advanced techniques in the preoperative as well as the intraoperative localization of the tumor site.

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Conflicts of interest

There are no conflicts of interest.

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