

Original Article**Unique Clinical Characteristics of Primary Hyperparathyroidism and Role of Nuclear Medicine Imaging**

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Abstract

Primary hyperparathyroidism (PHPT) has a variable clinical expression. Symptomatic PHPT is still the predominant form of the disease in many parts of the world, especially developing countries. Because the clinical profile of the disease has changed from that described in the past, we sought to improve our understanding of the disease in patients with unusual presentations and role of nuclear medicine imaging.

Materials and Methods- *We summarized the clinical presentation, biochemical, Nuclear medicine imaging and radiological features from the case records in the last six months of 7 patients at the apex hospital of Armed Forces (AHRR) who had documented as PHPT.*

Results: *N=7 (M2, F5), Mean age: 61.2 ± 14.6 years (38-76). Various clinical presentations as: Bony swelling, features of hypocalcaemia, recurrent kidney stones, recurrent fractures, osteoporosis, incidentaloma in USG neck.*

Torsades – de – pointes, multiglandular disease, Isolated Osteitis Fibrosa Cystica left maxilla and concurrent Paget's disease were unusual clinical characteristics.

99mTc MIBI scan was able to localize parathyroid adenoma in 5 out of 7 patients. Both USG and MIBI scan was not able to localize the lesion in one patient. In one patient MIBI scan does not localize the adenoma, however ultrasound (USG) reveals three hypoechoic lesions. ^{99m}Tc Methylene Diphosphonate (MDP) scan was done in 2 patients. Isolated bone lesion was detected in one patient and metabolic super scan was detected in another.

Conclusion: PHPT can have varied presentations. It continues to be a symptomatic disorder with skeletal and renal manifestation at younger age groups in India. MIBI parathyroid imaging is the most sensitive imaging modality in preoperative management. Additional single-photon emission computed tomography to planar scintigraphy provides information for localizing parathyroid lesions, to differentiate thyroid from parathyroid lesions. MIBI imaging is having limited role in multiglandular disease.

INTRODUCTION

Introduction

Primary hyperparathyroidism is characterized by the autonomous production of parathyroid hormone resulting in hypercalcemia. This is a common disease, occurring in about 1% of the adult population and about 2% of the population older than 55 y ⁽¹⁾. It occurs 2–3 times more frequently in women than in men.

Hyperparathyroidism peaks in incidence in the fourth and fifth decades of life but can occur in young children and the elderly as well ⁽²⁾.

Historically, patients presented with symptoms such as urolithiasis, bone pain, and pathologic fractures and non-specific symptoms such as depression, lethargy, and vague aches and pains. Since the advent of multichannel biochemical screening, however, patients frequently present without symptoms after being found to have hypercalcemia on routine laboratory screening ⁽³⁾. The frequency of this previously uncommon clinical scenario, an asymptomatic patient with hyperparathyroidism, has led to controversy and changes in the management of patients with this disease. These changes will be reviewed and further discussed in the “Treatment” section of this article.

In addition to causing these changes in the clinical presentation of primary hyperparathyroidism, technology has also led to changes in the treatments used for this disease. Surgery has been, and continues as, the most commonly used and successful treatment. The use of nuclear imaging, in combination with improved ultrasound imaging and the availability of rapid intra-operative parath-

yroid hormone assays, has changed the strategy of surgical treatment of primary hyperparathyroidism ^(3–5). Previously, the standard treatment for all patients with primary hyperparathyroidism was a bilateral neck exploration with the goal of identifying and evaluating 4 parathyroid glands. Visual inspection of the glands, sometimes used in conjunction with intra-operative histological assessment of frozen sections, allowed experienced surgeons to identify the pathologic glands and remove them with a success rate in excess of 90% ⁽³⁾. The ability to preoperatively localize pathologic parathyroid glands has enabled a more focused surgical approach.

Materials and Methods

We retrospectively studied the clinical presentation, biochemical, Nuclear medicine imaging and radiological features from the case records in the last six months of 7 patients at the apex hospital of Armed Forces who had documented as PHPT.

CASE SERIES

Case-1

- 38 yr old male.
- Admitted in ENT ward of our hospital with painless swelling left side of face.
- X-ray skull reveals osteolytic lesion with soft tissue component in left maxilla.
- FNAC of that site reported as Giant cell tumor (GCT).
- Based on few case reports association of GCT to parathyroid adenoma patient was referred to department of endocrinology.
- Patient was evaluated.

Investigation	Value	Normal range	Interpretation
S. Calcium	10.6 mg/dl	8.4-10.2	
S. Phosphorus	2.1 mg/dl	2.5-4.5	
S. Alkaline phos	157 IU/L	26-116	
i(PTH)	88 pg/ml	10-65	
25(OH)vit D	29 ng/dl	30-100	

Suggestive of primary hyperparathyroidism

Patient 1

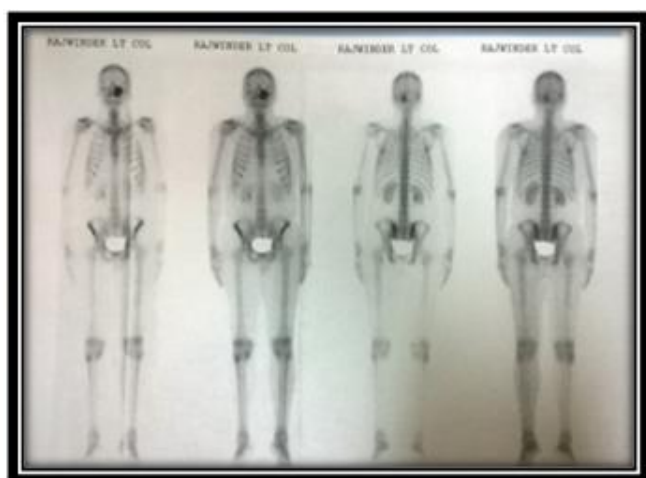


Figure 1 Tc99m MDP whole body bone scan shows increased osteoblastic activity in the region of left maxilla.

Patient 1



Patient 1

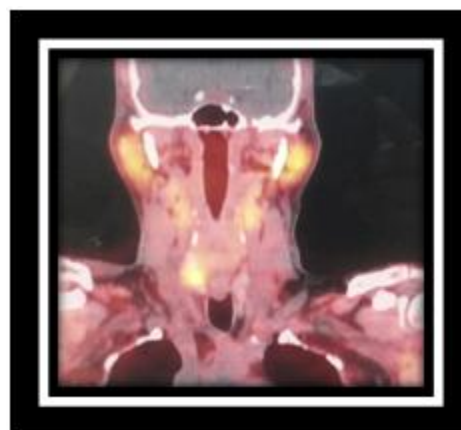


Figure 2 Tc99m Sestamibi scan with SPECT-CT (10/09/14): Delayed washout at superior pole of right thyroid lobe is suggestive of Right superior parathyroid adenoma(RSPA)

Final diagnosis

- PRIMARY HYPERPARATHYROIDISM
- RIGHT SUPERIOR PARATHYROID ADENOMA(RSPA).
- OSTEITIS FIBROSA CYSTICA (GIANT CELL REPARATIVE GRANULOMA - LEFT MAXILLA

CASE-2

- 58 yr female
- History of traumatic crush injury to left hand
- Crush syndrome – Acute kidney injury(AKI), hemodialysis was done
- Referred to AHRR in view of AKI

At AHRR	Patient 2	
<ul style="list-style-type: none"> • Cardiac arrest –revived • Hypokalemia (S. K⁺ - 2.2 mmol/L) was corrected • Recurrent episode of VT/VF requiring multiple defibrillations • Managed in CCU with Lignocaine, Amiodarone & Sotalol • Evaluation :short QT and hypercalcemia (S. Ca – 14.3 mg/dl) 	<p>ECG (BHDC)– Normal sinus rhythm with long QT</p> <p>Holter AHRR: short QT with Torsades- de - pointes</p>	

- Patient was referred to endocrinology department

Patient 2

Investigation	Value	Normal range	Interpretation
S. Creatinine	1.2 mg/dl	0.4 – 1	
Corrected Calcium	14.2 mg/dl	8.2-10.2	↑
S. Phosphorus	2.2 mg/dl	2.5-4.5	↓
S. Potassium	2.8 mmol/L	3.5 - 5	↓
S. Magnesium	1.9 mg/dl	1.5-2.5	↓
S. Alkaline phos	158 IU/L	26-116	↑

- Suggestive of primary hyperparathyroidism
- Patient was managed with careful IV fluids hydration, Inj Furosemide, potassium replacement, nasal Calcitonin 1 puff twice 12 hours apart and Inj. Zoledronic acid 4 mg IV stat.

i(PTH)	78 pg/ml	10-65	↑
25(OH)vit D	13 ng/dl	30-100	↓

Patient 2

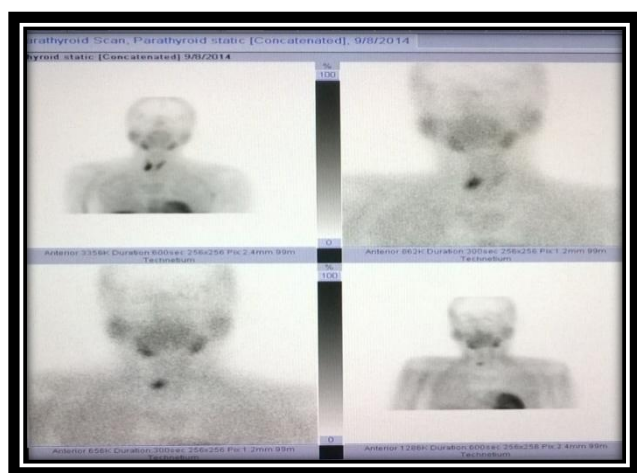


Figure 3 Tc99m Sestamibi scan shows hyperactive right superior parathyroid adenoma (RSPA)

Diagnosis

- CRUSH INJURY LEFT HAND: AKI (recovered)
- PRIMARY HYPERPARATHYROIDISM.
- RIGHT SUPERIOR PARATHYROID ADENOMA(RSPA)
- RECURRENT VT – TORSADES DE POINTES

CASE-3

- 76 yr female who was a known patient of COPD and Chronic AF. She started suffering from poor appetite x 3 months, progressive deterioration in sensorium x 10 days.
- Consulted Neurologist at Meerut
- Evaluation showed: BUN – 131 mg/dl, Creatinine – 3.4 mg/dl , S. Calcium – 12.8 (corrected – 13.6 mg/dl)
- NCCT & MRI Brain – NAD
- ECG – AF with FVR
- Managed with IV antibiotics, IV fluids, IV steroids, Calcitonin and oral diltiazem
- Referred to Endocrinology. Investigations were repeated, BUN – 101 mg/dl (6-20), Creatinine – 3.8 mg/dl (0.4-1), Corrected S. Calcium – 13.9 mg/dl (8.2-10.2) , S. Alk phosphatase – 114 U/L (26-116) , ECG – AF with FVR , i(PTH)- 312 pg/ml (10-65)
- Suggestive of primary hyperparathyroidism

Patient 3



Figure 4 Tc99m Sestamibi scan shows right inferior parathyroid adenoma(RIPA)

Diagnosis

- PRIMARY HYPERPARATHYROIDISM
- RIGHT INFERIOR PARATHYROID ADENOMA(RIPA)
- ATRIAL FIBRILLATION

CASE-4

- 49 yr/M
- Past history
 - Recurrent renal stone disease x 15 yrs
 - Primary HTN x 5 yrs
 - Non functioning Left kidney due to obstructive uropathy.
- Routine evaluation at Nephrology OPD showed
 - Hypercalcemia
 - Hypophosphatemia
- Referred to Endocrinology department.
- Medical management - Tab Cinacalcet 30mg twice daily

Patient 4



Figure 5-Tc99m Sestamibi scan shows Left superior parathyroid adenoma (LSPA)

Diagnosis

- RECURRENT RENAL STONE DISEASE
- PRIMARY HYPERTENSION
- PRIMARY HYPERPARATHYROIDISM
- LEFT SUPERIOR PARATHYROID ADENOMA(LSPA)

CASE-5

- 72 yr/F
- k/c/o Primary HTN x 10 yrs
- k/c/o Lumbar spondylosis, Degenerative Joint Disease
- Regular follow up at Rheumatology, Orthopedics and PMR(physiotherapy) department
- Referred to Endocrinology for BMD assessment

Investigation	Value	Normal range	Interpretation
BMD - DXA	T = - 2.1	-	Osteopenia
S. Creatinine	0.89 mg/dl	0.4 – 1	
S. Calcium	10.7 mg/dl	8.2-10.2	↑
S. Phosphorus	2.2 mg/dl	2.5-4.5	↓
S. Alkaline phos	132 IU/L	26-116	
24 hr urinary calcium	403 mg	< 200	↑
i(PTH)	145 pg/ml	10-65	↑
25(OH)vit D	31 ng/dl	30-100	

- Suggestive of primary hyperparathyroidism.
- USG and MIBI scan were not able to localize any adenoma
- Diagnosis: PRIMARY HYPERPARATHYROIDISM

CASE-6

- 50 yr, F
- Nephrologist
- Asymptomatic
- Routine evaluation showed
 - Hypercalcemia (S. Calcium – 11.2 mg/dl)
 - Sought Endocrinology consultation

Investigation	Value	Normal range	Interpretation
S. Creatinine	0.8 mg/dl	0.4 – 1	
S. Calcium	10.4, 10.9, 11.6 mg/dl	8.2-10.2	↑
S. Phosphorus	2.1 mg/dl	2.5-4.5	↓
S. Alkaline phos	146 IU/L	26-116	
i(PTH)	208 pg/ml	10-65	⬆
25(OH)vit D	32 ng/dl	30-100	

- Sestamibi scan: no adenoma localized
- USG neck: 3 hypoechoic lesions s/o parathyroid adenoma (LS, LI, RI)
- Advised further testing to r/o syndromic association in view of multiglandular disease

CASE-7

- 75 yr, F
- Presented with recurrent # on trivial trauma
- Osteopenia noted by treating Orthopedic surgeon
- Referred for evaluation of osteopenia
- Clinical examination at Endo OPD: enlarged head size noted
- Clinical impression: Paget's disease with osteopenia

Investigation	Value	Normal range	Interpretation
BMD - DXA	T = -3.2	-	Osteoporosis
S. Creatinine	0.69 mg/dl	0.4 – 1	
S. Calcium	11.2 mg/dl	8.2-10.2	↑
S. Phosphorus	2.3 mg/dl	2.5-4.5	↓
S. Alkaline phos	882 IU/L	26-116	↑
i(PTH)	96 pg/ml	10-65	↑



Figure-6 X ray skull: thickened calvarium,

Patient 7



Figure-7 X ray both bones rt leg: fracture shaft of tibia, osteopenia with likely bone cyst at lower end of femur and at fracture site

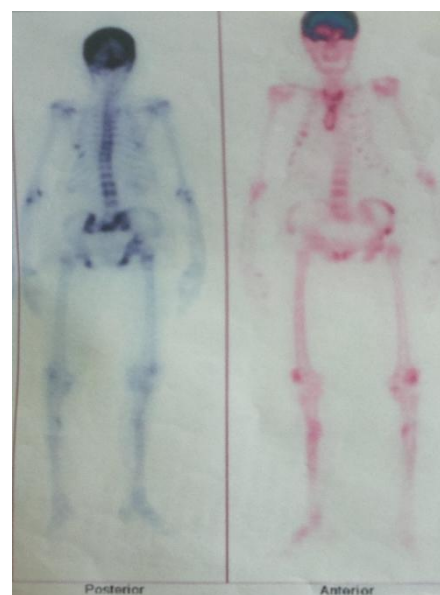
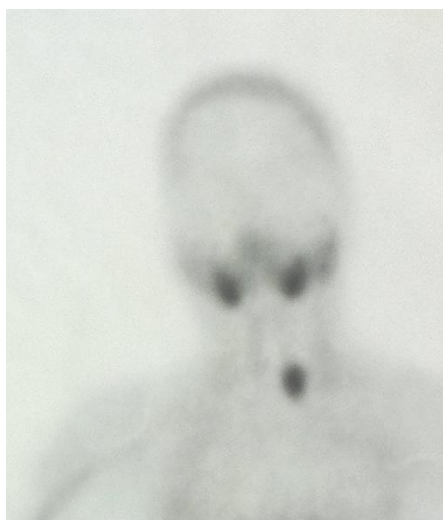


Figure-8 Bone scan: superscan with hypermetabolic area in the skull



Patient 7: Tc9m Sestamibi scan shows Left inferior parathyroid adenoma (LIPA)

Diagnosis

- Primary hyperparathyroidism.
- LEFT INFERIOR PARATHYROID ADENOMA (LIPA)
- Paget's disease and severe osteoporosis

Results

- N=7 (Male 2, Female 5)
- Mean age : 61.2 ± 14.6 years (38-76)
- Clinical presentation

Bony swelling	1 patient
Features of hypercalcemia	2 patient
Recurrent kidney stones	1 patient
Recurrent fractures	1 patient
Osteoporosis	1 patient
Incidental	1 patient

Unusual features

- Torsades – de – pointes=Association with hyperparathyroidism/ short QT syndrome has not been described



- Multiglandular disease
- Isolated OFC left maxilla-Localized form of fibrous-cystic osteitis in hyperparathyroidism, incidence 3- 5%. Common sites

of involvement are base of skull, orbits, paranasal sinuses, spinal column, tibia, humerus, clavicles, and mandible, rarely maxilla.

- Concurrent Paget's disease-Concurrent PHPT and Paget's disease described as isolated case reports only. Combination can be confusing as features overlap

Sr. No.	Calcium (8.2 – 10.2 mg/dl)	Phos (2.5 – 4.5 mg/dl)	ALP (20 - 116 IU/L)	iPTH (10 – 60 pg/ml)	25(OH) vit D (30 – 100 ng/ml)	Sesta mibi scan	USG neck
1.	10.6	2.1	157	88	27	RSPA	NA
2.	13.9	1.7	114	312	23	RIPA	NA
3.	14.2	2.2	158	78	13	RSPA	NA
4.	10.7	1.9	118	253	19	LSPA	NA
5.	10.7	2.2	132	145	31	-	-
6.	11.6	2.1	146	208	32	-	Multi glandula r
7.	11.2	2.3	882	96	-	LIPA	-
Mean	11.9 ± 1.7	2.1 ± 0.2	162.5 ± 16.8	180.7 ± 94.4	24.2 ± 7.3		

Discussion

There are few publications on PHPT from India when compared to that of countries like USA, UK, and Australia. The majority of these publications are case reports, small case series, and retrospective case series of approximately 100 cases. The majority (twenty one) of publications were from Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow (SGPGI-MS) which is quoted as benchmark in our study^[6,7]. Histogram Figure 1 shows the decade-wise publications from India since the first publication in 1980^[8]. The increase in the number of publications on PHPT between 2000–2010 compared to the previous decade is probably due to the increasing parathyroid awareness among the physicians; however, the number of publications are far less when compared to the developed countries. Histogram Figure 2 shows the comparative number of publications from India and the rest of the world.

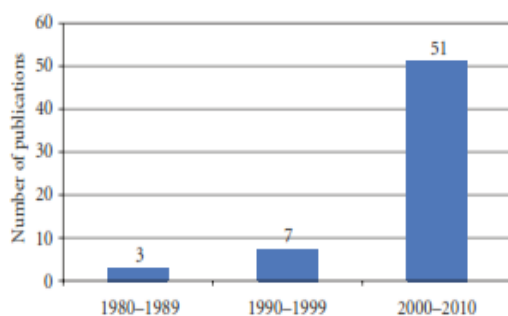


FIGURE 1: Decade wise publications on PHPT from India.

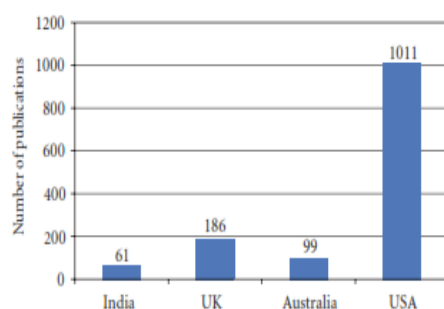


FIGURE 2: Publications on PHPT: India versus others.

P. V. Pradeep et al, International Journal of Endocrinology Volume 2011, Article ID 921814

TABLE 1: Clinical characteristics of Indian PHPT and the developed world.

	Total number of subjects for which data was available from India	Percentage affected (India)	Percentage affected (developed countries)*
Bone disease	344	77	5
Fractures	399	40.1	ND
Brown tumors	233	42	3
Renal disease	344	36	15
Proximal muscle weakness	357	54.1	ND
Pancreatitis	302	15	Nil
Psychiatric symptoms	246	26.4	ND
Asymptomatic disease	246	5.6	>80%

P. V. Pradeep et al, International Journal of Endocrinology Volume 2011, Article ID 921814

Multichannel autoanalyzers and routine screening of serum calcium levels has led to increase in prevalence of primary hyperparathyroidism (pHPT) between 0.1% and 0.4% [9]. There is a change in presentation of PHPT has changed from a symptomatic to an asymptomatic disease [10]. Thus newer guidelines are introduced to decide on indications for surgery in asymptomatic disease [11]. In India, however, asymptomatic presentation is rare.

There is limited literature on localization studies in all the Indian publications as compared to the published literature from Western series. Neck ultrasound (USG) has been reported to localize the adenoma in 65–77% of patients [12,13,14]. Methyl isobutyl isonitrile (MIBI) scan positivity has been reported in 86.9–100% [14,15]. Thallium-201 Technetium-99 pertechnetate subtraction has been reported to have a sensitivity of 87–100% [12,14,15]. Contrast-enhanced computerized tomography (CECT) of the neck has a sensitivity ranging from 65% to 93.5% in localizing parathyroid adenoma [12,13,14]. The reported sensitivity of ultrasound of the neck has been low in India, which could be due to the absence of a dedicated parathyroid sinologist. Therefore, the numbers of cases diagnosed/operated on are far less than what is reported from the developed nations [12,14,15,16]. Even though Thallium-201 Technetium-99 pertechnetate scan and CECT scan of the neck were more commonly used prior to the year 2000 for localization, these are currently replaced with MIBI and USG scan [17,18,19,20]. SPECT-CT also helps to localize the active parathyroid gland.

Conclusion

PHPT can have varied manifestations (asymptomatic to severe disease). A majority of patients diagnosed with PHPT in India have symptomatic disease as compared to west. The mean calcium, PTH and alkaline phosphate levels are high with low Vit D levels. Vit D deficiency contributes to the severity of bone disease. Interdisciplinary approach among general practitioner, nephrologist, rheumatologist, urologist, nuclear medicine physician, radiologist and endocrinologist is required for early diagnosis and management.

MIBI scan continues to be investigation of choice for pre-operative localisation of parathyroid adenoma. Planar images combined with SPECT-CT helps in more accurate localisation and to differentiate from thyroid swelling. In multiglandular disease sensitivity of MIBI scan falls.

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