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Original Article

Technetium-99m Sestamibi Scintigraphy Pattern in Patients with Secondary Hyperparathyroidism

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Abstract

Introduction: Metabolic bone disease is one of the major complications of end stage renal disease (ESRD). We aimed in this investigation to explore the role of Technetium-99m sestamibi (^{99m}Tc MIBI) scintigraphy in the pre-operative assessment of refractory hyperparathyroidism in hemodialysis (HD) patients.

Methods: Dual-phase ^{99m}Tc MIBI parathyroid scintigraphy was performed for 23 patients with ESRD who have persistent intact parathyroid hormone (iPTH) levels exceeding 300 pg/ml. Based on scintigraphy results, 13 patients underwent neck exploration during which only glands with positive scintigraphy findings were removed.

Results: Among the six patients who had iPTH levels < 800 pg/ml, only one patient had positive scintigraphy findings (16.7%). Among the 17 patients who had iPTH levels ≥ 800 pg/ml, 16 patients had positive scintigraphy findings (94.1%). ^{99m}Tc MIBI scan detected 23 positive sites of focal trace uptake in those 17 patients. Partial parathyroidectomy was performed for 13 patients, removing in total 19 glands, while four patients declined surgery. On histological examination, 12 glands showed diffuse hyperplasia, four glands showed nodular hyperplasia and three glands revealed parathyroid adenoma. The three glands with parathyroid adenoma were correctly identified prior to surgery by ^{99m}Tc MIBI scintigraphy. The long-term outcomes of these patients are now being monitored.

Conclusion: ESRD patients with iPTH level ≥ 800 pg/ml are more likely to have positive sites of focal tracer uptake on MIBI scan than patients with lower iPTH levels. Dual-phase ^{99m}Tc MIBI scintigraphy has the ability to correctly identify parathyroid adenoma prior to surgical exploration in these patients.

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Introduction

Secondary hyperparathyroidism (SHP) is one of the serious complications of end stage renal disease (ESRD) [1]. A number of factors may contribute to SHP, such as hypocalcemia, hyperphosphatemia, vitamin D deficiency and the reduction of vitamin D and calcium sensing receptors in the parathyroid gland [2]. Through poorly understood mechanisms, these factors lead initially to diffuse and polyclonal cell proliferation. Subsequently, in some glands, nodular growth occurs within diffuse hyperplastic tissue. These nodules represent autonomous and monoclonal growth, likely corresponding to the so-called 'tertiary hyperparathyroidism' [3].

Technetium-99m sestamibi (^{99m}Tc MIBI) scintigraphy is now widely used as an alternative method to thallium chloride-201 (^{201}TI) / ^{99m}Tc subtraction scintigraphy which is no longer used in clinical practice for imaging of parathyroid glands [4, 5]. Dual-phase ^{99m}Tc MIBI scan has demonstrated high specifity, despite low sensitivity, in locating parathyroid glands in patients with secondary hyperparathyroidism [6].

^{99m}Tc MIBI is concentrated within the cells through active transport and passive diffusion, a process facilitated by negative trans-membrane potential found in metabolically hyperactive cells and by the lipophilic nature of ^{99m}Tc MIBI [7]. As increased numbers of mitochondria have been found in hyperactive parathyroid cells, intra-mitochondrial sequestration may be an additional mechanism of ^{99m}Tc MIBI tissue binding [7]. This may account for slower ^{99m}Tc MIBI washout from hyperactive parathyroid compared to normal thyroid and parathyroid tissues [8].

The aim of the present study was to evaluate the role of dual-phase ^{99m}Tc MIBI scintigraphy in the pre-operative

Table 1: Clinical and biochemical data, scintigraphy findings and histological diagnosis of studied patients

No	Age (years)	HD duration (months)	Phosphorus (mg/dl)	Calcium (mg/dl)	iPTH (pg/ml)	Scintigraphy result	Site and number of positive glands	Histological pattern
1	52	20	4.7	7.2	330	Negative	-	-
2	48	45	4.4	8.5	340	Negative		
3	56	50	4.3	7.8	341	Negative	-	-
4	45	40	4.8	8.3	535	Negative	-	-
5	30	36	4.5	9.0	560	Negative	-	-
6	27	108	8.2	9.5	780	Positive	RL (1)	DHP
7	63	90	4.5	7.7	890	Positive	LL (1)	DHP
8	65	120	5.0	8.3	933	Negative	-	-
9	63	108	8.2	9.5	966	Positive	LL (1)	DHP
10	63	118	8.2	9.5	1000	Positive	LL (1)	DHP
11	50	125	4.6	7.3	1055	Positive	RL+LL (2)	NHP
12	40	132	4.8	7.7	1078	Positive	RL (1)	-
13	60	90	7.4	9.1	1120	Positive	RL+LL (2)	NHP
14	70	120	4.8	10	1200	Positive	LU (1)	AD
15	63	108	2.5	9.5	1200	Positive	LL (1)	-
16	63	120	4.5	9.2	1200	Positive	RL+LL (2)	NHP
17	50	85	4.0	9.5	1215	Positive	RL+LL (2)	NHP
18	63	80	3.9	10.2	1500	Positive	LL (1)	-
19	60	100	2.2	10.2	1550	Positive	RL (1)	AD
20	40	132	3.8	9.4	1712	Positive	RL+LL (2)	NHP
21	58	90	4.9	9.8	1800	Positive	RL (1)	-
22	40	180	4.8	10.3	2000	Positive	RL (1)	AD
23	60	96	5.5	8	2161	Positive	RL+LL (2)	NHP

DHP = Diffuse Hyperplasia, NHP = Nodular Hyperplasia, AD = Adenoma, LL = Left Lower, RL = Right Lower, LU = Left Upper

assessment of parathyroid glands of uremic patients with refractory hyperparathyroidism.

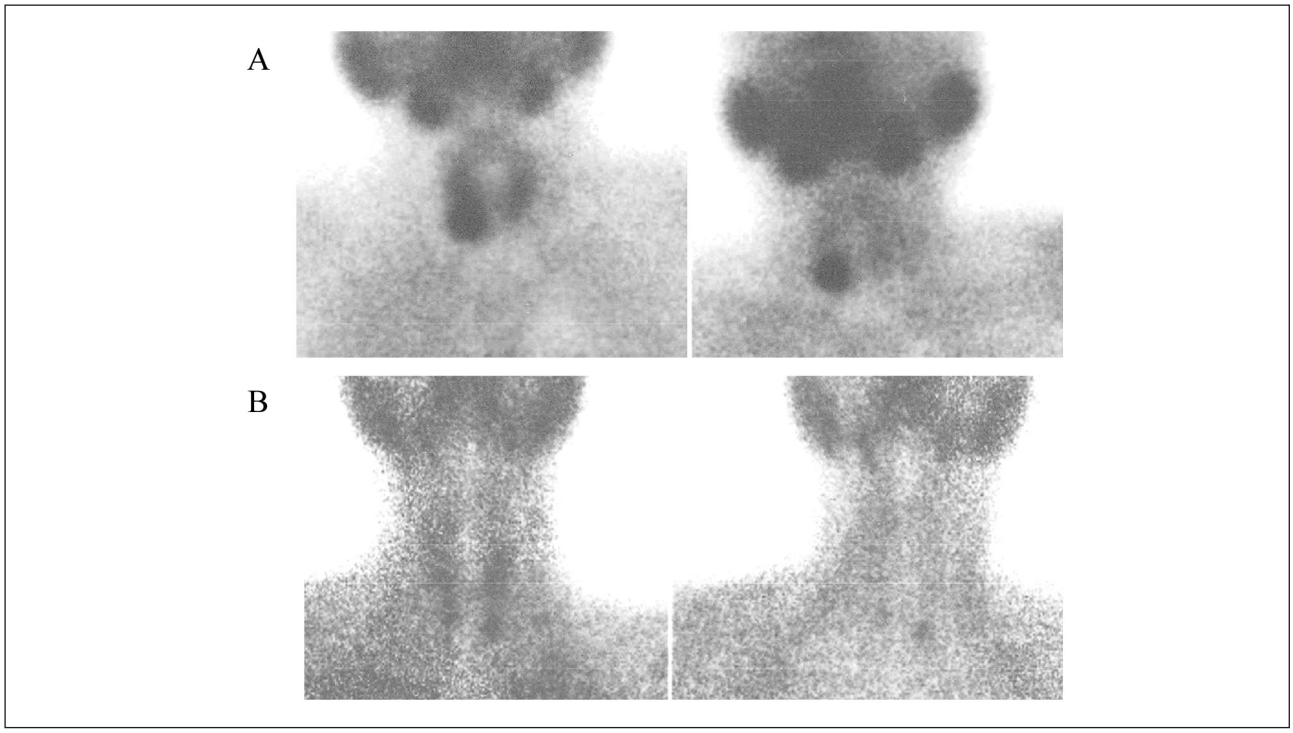
Methods

The study included ESRD patients maintained on regular hemodialysis (HD) who had persistent intact parathyroid hormone (iPTH) levels more than 300 pg/ml using specific radioimmunoassay. Informed consent was obtained from all patients for a dual-phase ^{99m}Tc MIBI scan. Fifteen mCi (550 MBq) of ^{99m}Tc MIBI was intravenously injected in all patients. Twenty minutes post-injection, planar anterior imaging of the neck and the upper thorax of supine patients was performed (early phase) using a large field gamma camera with low-energy, high resolution, parallel-hole collimator, 20% energy window centered at 140 Kev, 128x128 matrix for static images and zoom 2.65. The second phase (delayed phase) was performed two hours after the injection of ^{99m}Tc MIBI. Scans were performed on the following day of a dialysis session. All patients had preliminary ^{99m}Tc pertechnetate thyroid scintigraphy performed one week earlier to exclude the presence of thyroid hot nodules or other focal lesions in the thyroid gland. Images were separately scrutinized by two nuclear medicine physicians for foci of abnormally active trace uptake in the expected location of parathyroid glands or other ectopic sites. Patients with positive scintigraphy findings were referred for partial parathyroidectomy, removing only glands identified to have active foci of trace uptake. Unpaired Student's t test was used to compare means and Chi square test was used to compare proportions. P value < 0.05 was considered statistically significant.

Results

The study group included 23 patients with ESRD and refractory hyperparathyroidism. Their mean age was

Figure 1: Dual phase 99mTc MIBI scan at 20 min (early phase) on the left and at 2 hours (delayed phase) on the right in two patients with uremic hyperparathyroidism: (A) shows right lower parathyroid gland adenoma and (B) shows bilateral lower parathyroid glands hyperplasia



53.4 years (SD 11.7; range 27-70 years). Patients have been on regular HD for a mean duration of 95.3 months (SD 37.4; range 20-180 months). The majority of patients presented with variable symptoms and signs related to metabolic bone disease despite regular treatment with calcium carbonate and calcitriol. This treatment was not interrupted during the course of the present study. The mean pre-dialysis concentration of serum calcium was 8.9 mg/dl (SD 1; range 7.2-10.3 mg/dl) and the mean pre-dialysis concentration of serum phosphorus was 4.9 mg/dl (SD 1.6; range 2.2-8.2 mg/dl). The mean level of circulating iPTH was 1107 pg/ml (SD 512; range 330-1161 pg/ml), assayed by specific radioimmunoassay. Clinical and biochemical data of individual patients are summarized in Table 1.

Thyroid scintigraphy was normal in all patients. Early phase ^{99m}Tc MIBI scintigraphy showed normal thyroid uptake in all cases associated with focal extra-thyroid hot spots in the anatomical sites of parathyroid glands region in scintigraphy positive cases. In the delayed phase, ^{99m}Tc MIBI uptake in the thyroid decreased while its relative focal concentration increased in the parathyroid tissue. Two examples of ^{99m}Tc MIBI positive parathyroid scans are shown in Figure 1.

Overall, ^{99m}Tc MIBI scan detected 23 positive sites of focal trace uptake in the 17 patients with positive findings. Among the six patients who had iPTH level < 800 pg/ml, only one patient had positive scintigraphy findings (16.7%). Among the 17 patients who had iPTH level ≥ 800 pg/ml, 16 patients had positive scintigraphy findings (94.1%).

Patients with positive ^{99m}Tc MIBI scintigraphy scans had higher mean iPTH concentrations (1319±400 versus 507±233 pg/ml, $P < 0.0001$), higher mean serum calcium concentration (9.2±0.9 versus 8.2±0.6 mg/dl; $P = 0.01$), and longer mean dialysis duration (111±24 versus 52±35 months; $P < 0.0001$) compared to those with negative scans. Age and serum phosphorus level were not significantly different between the two groups.

Thirteen patients with positive ^{99m}Tc MIBI scintigraphy findings had partial parathyroidectomy, removing in total 19 glands with focal trace intake, while four patients declined surgery. On histological examination of these glands, 12 glands showed diffuse hyperplasia (increased number of parenchymal cells with normal lobular structures), four glands showed nodular hyperplasia (at least one well circumscribed, encapsulated and virtually fat cell-free accumulation of parenchymal cells) and three glands revealed parathyroid adenoma. ^{99m}Tc

MIBI scintigraphy correctly identified the three glands with parathyroid adenoma prior to surgery. In addition, glands found to have nodular hyperplasia had higher trace uptake during scintigraphy and were associated with higher iPTH levels (> 1000 pg/ml) than glands with diffuse hyperplasia. The long-term outcomes of patient who underwent partial parathyroidectomy and those who declined surgery are now being monitored.

Discussion

Significant morbidity and mortality can result from SHP in patients with ESRD [9]. The Kidney Disease Outcomes Quality Initiative (K/DOQI) Guidelines define parathyroid over-activity in ESRD patients by an iPTH level > 300 pg/ml. The same guidelines recommend parathyroidectomy for patients with persistent levels of iPTH > 800 pg/ml, associated with hypercalcemia and/or hyperphosphatemia that are refractory to medical therapy [10].

Abnormal parathyroid glands can be located using various techniques in patients with SHP. ^{99m}Tc MIBI scintigraphy has higher sensitivity and specifity than ultrasound in case of SHP [6]. Slower MIBI washout has been observed in hyperactive parathyroid glands compared with normal thyroids and parathyroids [11]. Piga *et al* stated that ^{99m}Tc MIBI scans do not simply reveal parathyroid enlargement but rather identify hyperfunctioning parathyroid glands in uremic patients with SHP [12]. In the present study, ^{99m}Tc MIBI detected hyper-functioning glands in 17 out of 23 HD patients with SHP (73.9 %). Custodio *et al* demonstrated that 88.8% of their 18 patients with SHP had hyperactive glands on ^{99m}Tc MIBI scan [13]. An important factor that may influence the rate of positive scintigraphy findings in patients with SHP and parathyroid adenoma is the variable expression of metabolism transporters, such as p-glycoprotein (P-GP) or multidrug resistance-associated protein (MRP) in the parathyroid glands, which may function as a drug transporter for ^{99m}Tc MIBI [14, 15]. In our opinion, SPECT technique may increase the sensitivity of ^{99m}Tc MIBI scan in detecting hyper-functioning parathyroid glands compared to planar images.

In the current study, we observed that patients with positive ^{99m}Tc MIBI scans had higher iPTH concentrations and longer duration on dialysis compared to patients with negative scans. This concurs with the findings of previous reports [12, 13, 16]. The association between high trace uptake and nodular hyperplasia on histological examination in this study was expected. It is well known that glands with nodular growth patterns are heavier and show higher proliferative activity than diffusely hyper-plastic glands [17, 18]. Torregrosa *et al* demonstrated that ^{99m}Tc MIBI scintigraphy accurately reflects the functional status of the hyper-plastic parathyroid glands, with higher uptake grades correlating with the active growth phase [19].

According to the K/DOQI guidelines, effective surgical therapy of severe hyperparathyroidism can be accomplished by subtotal parathyroidectomy or total parathyroidectomy with parathyroid tissue autotransplantation [10]. We referred patients with positive scintigraphy findings for partial parathyroidectomy, removing only glands identified to have active foci of trace uptake. The long-term outcomes of these patients are now being monitored.

Conclusion

In addition to biochemical data, ^{99m}Tc MIBI parathyroid scan can be a useful screening method to assess the functional status of parathyroid glands in uremic patients with secondary hyperparathyroidism as well as to detect functional autonomy (tertiary hyperparathyroidism).

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