Parathyroid nuclear scan. A focused review on the technical and biological factors affecting its outcome

Subramanian Kannan
Mira Milas
Donald Neumann
Rikesh T. Parikh
Alan Siperstein
Angelo Licata

1 Fellow in Endocrinology, Cleveland Clinic Foundation, Cleveland, OH, USA
2 Department of Endocrine Surgery, Cleveland Clinic Foundation, Cleveland, OH, USA
3 Department of Nuclear Medicine, Cleveland Clinic Foundation, Cleveland, OH, USA
4 Department of Endocrinology, Cleveland Clinic Foundation, Cleveland, OH, USA

Address for correspondence:
Angelo Licata, MD
9500 Euclid Avenue Desk F20
Cleveland OH 44195, USA
Phone: 216-444-6248
Fax: 216-445-1656
E-mail: licataa@ccf.org

Summary

Objective. Technetium Parathyroid Scintigraphy (TS) is the most popular noninvasive localization procedure in patients with primary hyperparathyroidism (PHPT). Awareness of various factors involved in technetium uptake helps understand the outcome of TS.

Methods. We utilize a case of changing TS scans in a patient to review the literature on the various biological and technical factors involved in technetium uptake that could result in negative scan in parathyroid nuclear scintigraphy.

Results. Technical factors like the type of Tc isotope used, imaging techniques and biological factors like biochemical parameters (calcium, vitamin D levels), adenoma size, content of oxyphilic cells, vascularity can affect the outcome of the scan.

Conclusion. Clinicians should be aware of technical and biological factors that could result in negative scan in parathyroid nuclear scintigraphy.

KEY WORDS: primary hyperparathyroidism; parathyroid nuclear scintigraphy; technetium tetrofosmin; technetium sestamibi.

Introduction

Technetium nuclear scintigraphy (TS) is the most popular procedure to localize abnormal parathyroid glands in patients with primary hyperparathyroidism (PHPT). The two radio-pharmaceuticals used are 99mTc-Sestamibi and 99mTc-Tetrofosmin. Despite its limitations and variable accuracy TS along with pre-operative ultrasound has an established role in centers which perform large volume parathyroid surgery (1, 2). However there are technical and biological factors that affect the uptake of the 99mTc in the parathyroid adenoma and potentially affect the sensitivity and specificity of scan. We present a patient with PHPT whose initially negative scan converted to a positive scan five years later. We then review published data about the biological and technical factors that could possibly lead to such conversion.

Case report

A 63 year old Caucasian woman was evaluated in 2005 for high normal calcium 10.2 mg/dl (8.5-10.5), elevated PTH (72 pg/ml) and low bone mineral density (BMD) in the spine (T-score -1.5) and the hip (T-score -1.3). Information on forearm bone density was not available. She had no problems attributable to parathyroid disease. Her daily total calcium intake was approximately 2500mg including diet and supplements and 400-800 IU vitamin D/day from Multivitamins. Her examination was normal. The initial laboratory test results are listed in Table 1. A 99mTc scan using 99mTc-Tetrofosmin showed no definite areas of abnormal uptake to suggest possible sites for abnormal parathyroid tissue (Figure 1).

Neck Ultrasound (US) did not reveal enlarged parathyroid lesions. A repeat scan using 99mTc-Sestamibi revealed hypervascular parathyroid lesion in the right lower neck. She underwent successful removal of a right lower parathyroid adenoma.

Key Words: primary hyperparathyroidism; parathyroid nuclear scintigraphy; technetium tetrofosmin; technetium sestamibi.
and pockets of clear cells. Her calcium and PTH levels normalized after surgery (Table 1).

Discussion

Our case provided the unique opportunity to compare two different radio-pharmaceuticals of 99mTc based scans in the natural history of PHPT. Multiple factors could explain the conversion of the TS from a initial negative scan to a positive scan including disease progression, increase in size and vascularity of the adenoma, change in radio-pharmaceuticals of 99mTc and variability in technique of the two scans.

We now review the biological and technical factors that can potentially affect the outcome of TS:

I. Biological factors affecting TS:

Sestamibi and Tetrofosmin are monovalent lipophilic cations that diffuse passively down an electro-chemical gradient through cell membranes and accumulate almost exclusively in mitochondria of parathyroid lesions. A normal parathyroid gland does not take up Sestamibi or Tetrofosmin. The exact mechanism of its selective uptake in abnormal parathyroid glands remains debatable. High mitochondrial activity is considered to be the major component of tracer uptake by human parathyroid tissue in patients with PHPT (3). The following factors have been reported to be associated with negative scans.

a. Biochemical factors:

i. Serum calcium level

Higher preoperative calcium levels are more likely to be observed in patients with positive scans. In a study of 102 patients, more than 95% of those with plasma calcium greater than 11.3 mg/dL had a positive scan as compared with 60% of those with lesser values (4).

ii. Serum PTH level

A significant correlation was noted between the uptake and preoperative PTH levels. Higher PTH values are more likely observed in patients with positive scans (5). A serum PTH level greater than 160 pg/mL correlated with positive scans in 93% as opposed to 57% in those with lower levels (4). This correlation was not observed by others and the overlap of PTH levels in positive and neg-

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Parathyroid nuclear scan

Figure 1 - Initial nuclear parathyroid scintigraphy using Tc-Tetrofosmin.

Figure 2 - Second nuclear parathyroid scintigraphy using Tc-Sestamibi (arrows point to abnormal right lower parathyroid).
S. Kannan et al.

iv. Multi-gland disease

a. Evolution of TS:

Technical aspects for TS have evolved in recent years. The first radionuclide imaging technique widely used in the 1980s for hyper-functioning parathyroid localization was thallium-201 (201Tl) scintigraphy. Since 201Tl was taken up by both the thyroid and parathyroid, it was used in conjunction with 99mTc pertechnetate, which is taken up only by the thyroid (16). The 99mTc scintigram then was digitally subtracted from the 201Tl scintigram to allow parathyroid localization. In 1989, Coakley and colleagues reported the use of 99mTc Sestamibi for parathyroid scintigraphy (17). It was a serendipitous discovery as 99mTc was predominantly used in cardiac stress testing during those days. The new radionuclide rapidly replaced 201Tl because of superior image quality, more favorable dosimetry, and improved detection sensitivity (18). Variations of this basic methodology have since been used in practice which includes single-isotope dual-phase imaging and dual-isotope subtraction imaging.

The single-isotope dual-phase (early and delayed phase) scintigraphic technique was suggested by Taillefer et al based on the observation that 99mTc-Sestamibi washes out more rapidly from the thyroid gland than from hyper-functioning parathyroid glands (19). The neck is imaged at 5 minutes and 120 minutes after 99mTc-Sestamibi administration. The “differential washout” phenomenon improves target-to-background activity so that abnormal parathyroid tissue should become more visible on the delayed images. In the dual agent method thyroid images obtained with Iodine-123 (123I) or 99mTc pertechnetate are subtracted from the images obtained with 99mTc Sestamibi thereby revealing persistent isotope uptake in the parathyroid adenoma.

b. Imaging techniques in TS:

These changes in Tc agents were followed by improved imaging methods. Planar imaging (2 dimensional) was followed by tomographic (3 dimensional) imaging. The advantages of single photon emission computed tomography (SPECT) over planar imaging included an enhanced contrast, 3-dimensional localization, and estimation of lesion size. SPECT was found to further increase the sensitivity of parathyroid imaging from 87% (as in planar scintigraphy) up to 95% (20). The introduction of hybrid SPECT/CT, an instrument that physically couples a SPECT camera with a CT in a single integrated unit offers the potential advantage of better anatomically defining the location of scintigraphic findings that are identified on SPECT images. Another addition to parathyroid imaging has been the 4D-CT also referred to as multidimensional CT. Its difference compared to a 3D CT is the fourth dimension with contrast enhancement. Parathyroid adenomas typically enhance avidly on early-phase imaging, and the hyper-enhancement persists despite a long delay after contrast administration. The degree of early enhancing and slow washout of contrast correlates with metabolic activity of the parathyroid adenoma. This characteristic gives 4D-CT the double advantage of demonstrating gland functionality and excellent anatomy of the gland and its surrounding structures.

c. Isotope-Tracers of Technetium:

99mTc-Sestamibi and 99mTc-Tetrofosmin are both used in TS. Often, the choice of imaging agent depends on its availability, which agent is used for cardiac stress testing in the institution and the experience of the physician.

28
Parathyroid nuclear scan

Table 2 - Biochemical and biological factors affecting the likelihood of positive TS.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Higher Likelihood of Positive Tc scan</th>
<th>Lower Likelihood of Positive Tc scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium level (mg/dl)</td>
<td>Greater than 11.3</td>
<td>Lesser than 11.3</td>
</tr>
<tr>
<td>PTH level (pg/ml)</td>
<td>Greater than 160</td>
<td>Lesser than 160</td>
</tr>
<tr>
<td>25 Hydroxy Vitamin D (ng/dl)</td>
<td>Lesser than 25</td>
<td>Greater than 25</td>
</tr>
<tr>
<td>Use of Calcium Channel Blocker</td>
<td>Non-use of CCB</td>
<td>Use of CCB</td>
</tr>
<tr>
<td>Mean weight of Adenoma (mg)</td>
<td>Greater than 20%</td>
<td>Lesser than 20%</td>
</tr>
<tr>
<td>Oxyphil cell content</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3 - Summary of the studies comparing Tetrofosmin and Sestamibi.

| Author & Year     | Type of Study | PHTP patients (n) | Type of Scan technique                           | Results                                                        |
|-------------------|---------------|-------------------|--------------------------------------------------|                                                               |
| Agner et al 199623| Prospective   | 10                | Single agent dual phase                          | Sensitivity of Tetrofosmin comparable to Sestamibi            |
| Giordano et al 199721| Prospective | 93                | Single agent dual phase & Per-technetate subtraction | Correct result 88% (S) vs 59% (T) (P=0.016)                  |
| Wakamatsu et al 200122| Prospective | 25                | Dual agent Subtraction; Parallel hole collimator | SGD: 63.2% (T) vs 68.4% (S) MGD: 41.7% (T) vs 41.7%(S)    |
| A C Froberg et al 200224| Retrospective | 8                 | Single agent dual phase; Planar images            | 8/8 cases: 100% (S) 2/8 cases: 25% (T)                      |

**T= Tetrofosmin; S=Sestamibi**

Giordano et al compared the retention characteristics of these two tracers and Tc-technetate in euthyroid subjects and found that Tc-Tetrofosmin had a lower early thyroid uptake than 99mTc-Sestamibi (2.26±0.52 vs. 2.01±0.49, respectively; p<0.002) as well as lower retention (1.4±0.37 vs. 1.65±0.58, respectively; p<0.002) (21). This finding provided an objective basis for the poorer results of 99mTc-Tetrofosmin in single agent dual phase parathyroid scintigraphy. However Wakamatsu et al. found that the two isotopes had similar sensitivities in the dual agent subtraction technique: 51.2% (Tetrofosmin) versus 53.5% (Sestamibi) in overall sensitivities, 63.2% vs 68.4% (single gland disease), 41.7% versus 41.7% (multi-gland disease)(22). Table 3 summarizes the studies comparing Tetrofosmin and Sestamibi (23, 24).

In the index case described serum biochemical markers were comparable during both the scans. It is possible that the adenoma increased in size, vascularity and had accrued more oxyphil cells along with changes in the cell surface glycoproteins in the 5 year time period. However these factors are impossible to evaluate and objectively compare. Lack of information on the forearm bone density during the initial scan makes it difficult to say with certainty whether her osteoporosis had worsened. Addition of CT to SPECT imaging during the second scan did not contribute to the conversion in our case as the adenoma was clearly visible even on the initial SPECT images (Figure 2). The biggest technical factor that was different between the two scans was the type of isotope tracer used. The differences in tumor localization ability between Tetrofosmin and Sestamibi was compared in a prospectively maintained database of sporadic PHPT patients from 2004-2006 at the Cleveland Clinic (Institution quality outcome survey, internal data not previously published). The patients were divided into two groups depending on the isotope used (Sestamibi (n=262) & Tetrofosmin (n=83)) and the accuracy of localization was adjusted to age, gender, BMI and gland size. Sestamibi and Tetrofosmin didn't show any difference in overall accuracy when a single adenoma or multigland hyperplasia was noted. However when the scan showed a single gland, Tetrofosmin was significantly less accurate in orienting the surgeon to the diseased gland than Sestamibi (Tetrofosmin 64%, Sestamibi 79%; χ² test 10.3; p 0.01). This led to a change of practice at the Cleveland Clinic where Tc-Sestamibi is routinely used for pre-operative localization.

**Conclusion**

Changing TS from negative to positive is an interesting phenomenon and the various biological and technical factors help us understand the process involved in 99mTc-isotope uptake by abnormal parathyroid cells. It is important to emphasize that diagnosis of PHPT is made on clinical and biochemical data. TS is not a diagnostic tool. Its imaging capabilities are limited and the surgeon’s skill is the ultimate “localizing test”. By understanding the technical and biological factors involved in imaging and possibly manipulating some or all of them in the future, the accuracy of these scans may
markedly improve. Clinicians should be aware of technical and biological factors that could result in negative scan in TS.

References


