Appearance of Ectopic Undescended Inferior Parathyroid Adenomas on Technetium Tc 99m Sestamibi Scintigraphy

A Lesson From Reoperative Parathyroidectomy

David Axelrod, MD; James C. Sisson, MD; Kyung Cho, MD; Judiann Miskulin, MD; Paul G. Gauger, MD

Hypothesis: Critical postoperative review of technetium Tc 99m sestamibi scintigraphy can identify an undescended parathyroid adenoma on scans initially interpreted as nondiagnostic or negative.

Design: Case series.

Setting: A single, tertiary care academic medical center.

Patients: Three patients with persistent hyperparathyroidism.

Intervention: Technetium Tc 99m sestamibi scanning.

Outcome Measure: Medical records, operative reports, selective venous sampling results, and sestamibi scans were reviewed to identify scintigraphic findings diagnostic of an undescended parathyroid adenoma.

Results: All patients were cured of their persistent or recurrent hyperparathyroidism during reoperation by resection of an undescended inferior parathyroid adenoma. Subsequent review of the preoperative sestamibi scans demonstrated scintigraphic evidence of the undescended adenoma. In each case there was asymmetry in the physiologic activity attributed to the ipsilateral submandibular gland that, in fact, corresponded to an ectopic parathyroid adenoma at the level of the carotid bifurcation.

Conclusions: Careful attention to the contour of radioactivity in the region of the submandibular salivary gland may alert surgeons to the presence of an undescended inferior adenoma. After corroboration, this finding may facilitate a targeted operation.

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Primary hyperparathyroidism is the most common cause of elevated calcium levels in the outpatient population, affecting more than 100,000 Americans per year and 1 in 500 women older than 40 years. The majority of hyperparathyroidism is caused by a single enlarged parathyroid adenoma (85%), while the remainder is due to multigland disease (13%). Surgical excision results in eucalcemia in greater than 95% of patients who undergo a standard parathyroidectomy (4-gland exploration). Although a 4-gland exploration remains the gold standard procedure, surgeons, partially driven by patient demand and market forces, during the past 5 years have increasingly shifted toward targeted or minimally invasive surgical procedures. These limited procedures may use adjunctive technologies like intraoperative radioguidance, small endoscopic equipment, or intraoperative parathyroid hormone monitoring.

Successful and accurate preoperative imaging to localize the culprit adenoma(s) is crucial to the success of any targeted or minimally invasive parathyroidectomy procedure. The 2 most common techniques are high-resolution cervical ultrasound and technetium Tc 99m sestamibi scintigraphy (sestamibi). Success of sestamibi scintigraphy has been variable, with some centers reporting positive predictive values approaching 100% in identifying abnormal parathyroid glands. However, sestamibi scans are falsely negative in 11% to 33% of cases in which a single adenoma is ultimately identified. Until the recent shift toward minimally invasive procedures, preoperative sestamibi localization had been discouraged as a costly, unnecessary procedure that should be restricted to reoperative surgery. Thus, much of the literature on the technique is derived from this difficult patient population. In the primary setting, sestamibi scanning may be less sensitive (because of an unselected patient population) but, if positive, is generally accurate for glands in the standard anatomic positions.
The aim of this report is to illustrate how postoperative review of sestamibi scintigraphy by both the nuclear medicine physician and the operating surgeon can refine the interpretation of the scans and eventually improve therapy for patients with hyperparathyroidism. Specifically, we describe 3 patients in whom a reproducible finding on sestamibi imaging was identified that may identify undescended parathyroid adenomas. Preoperative recognition of the presence of this undescended gland may influence the subsequent operative approach in the reoperative setting or potentially even the primary setting.

METHODS

During a 2-year period at a single institution, 3 patients were cured of their persistent or recurrent hyperparathyroidism during reoperation with resection of an ectopic undescended inferior parathyroid adenoma. These operations were performed with the patient under general anesthesia, and each patient remained in the hospital for at least 24 hours of monitoring. These 3 patients all had the operative finding of a parathyroid adenoma within the carotid sheath near the arterial bifurcation. The adenoma was pathologically confirmed in each case. A review was conducted for diagnostic and operative details. All sestamibi scans were again reviewed and found to have focal and transient asymmetry in the region of the ipsilateral submandibular salivary glands corresponding to the location of the adenoma. All findings were interpreted in the context of clinical data from selective venous sampling for intact parathyroid hormone (iPTH). The project was reviewed and found to have focal and transient asymmetry in the region of the ipsilateral submandibular salivary glands corresponding to the location of the adenoma. All findings were interpreted in the context of clinical data from selective venous sampling for intact parathyroid hormone (iPTH). The project was reviewed by the institutional review board and determined to be exempt from ongoing oversight.

SESTAMIBI SCINTIGRAPHY

Sestamibi scanning was conducted by means of a standardized imaging protocol with 20 mCi (740 MBq) of technetium Tc 99m sestamibi administered intravenously. A large-field-of-view scintillation camera with a low-energy, high-resolution, parallel-hole collimator was used with a 20% window centered on the 140-keV photo peak. Patients were imaged in the supine position with the neck extended and immobilized for 10 minutes for anteroposterior, right anterior oblique, and left anterior oblique views. Single-photon emission computed tomographic (SPECT) images were also collected. The delayed images were obtained in the same views at 2 to 4 hours after injection to allow thyroid washout. It is important to note that both submandibular and parotid salivary glands concentrate and retain sestamibi. Therefore, these structures are nearly always seen during sestamibi scanning.

SELECTIVE VENOUS SAMPLING

After the patients gave informed consent, vascular access was obtained and the right internal jugular, right superior thyroid, right innominate, left innominate, left superior intercostal, left internal jugular, left superior and middle thyroid, left subclavian, and azygos veins; right hepatic vein; inferior vena cava; right and left iliac veins; and thymic vein were selectively catheterized and blood samples were sent for assay of iPTH. Patients were then discharged to home after recovery and assurance of hemostasis.

RESULTS

Patient 1 was a 40-year-old man with complaints of bone and joint aches and biochemical evidence of hyperparathyroidism. At presentation, his serum calcium level was 11.9 mg/dL (3.0 mmol/L) and his intact parathyroid hormone (iPTH) level was 106 pg/mL. A preoperative sestamibi scan failed to localize an adenoma. The patient underwent a standard 4-gland exploration that failed to disclose a left inferior parathyroid gland. The other 3 parathyroid glands were morphologically normal and were in standard anatomic positions. A cervical thymectomy and subtotal resection of the left thyroid lobe failed to demonstrate the adenoma. The left carotid sheath was explored to the level of the bifurcation and the adenoma was not located. The surgical wound was then closed with a presumptive diagnosis of an ectopic mediastinal adenoma.

Postoperatively, another sestamibi scan was obtained (Figure 1 and Figure 2). Although this scan was initially interpreted as nondiagnostic, subsequent review detected a focus of radioactivity in the region of, and in addition to, radioactivity in the left submandibular salivary gland. Selective venous sampling identified the site of parathyroid hormone hypersecretion high in the left side of the neck (Table). Ultrasonographic examination of the left cervical region showed a hypoechoic mass in the left carotid sheath located 1 cm inferior to the angle of the jaw that measured 2 cm in greatest diameter. The patient was then returned to the operating room and underwent a directed exploration through a small incision under the angle of the mandible. A 2.0-g adenoma was identified slightly cephalad to the carotid bifurcation and was removed without difficulty. After this operation, his serum calcium level returned to normal.

Patient 2 was a 76-year-old woman with a long-standing history of primary hyperparathyroidism. She had undergone standard 4-gland exploration elsewhere several years before referral, at which time no left inferior gland was identified, despite cervical thymectomy and subtotal thyroidectomy. Postoperatively, she had persistent hyperparathyroidism with a calcium level of 11.1 mg/dL (2.8 mmol/L) and an iPTH level of 160 pg/mL. Before reexploration, the patient underwent sestamibi...
scanning to identify her missing adenoma. This scan (Figure 3) demonstrated tracer in the right inferior thyroid pole that failed to persist on the delayed scan. She was known to have residual thyroid tissue in that region. This radioactive focus was considered a false-positive finding (in relation to parathyroid disease), because the area of uptake did not correlate with the results of her iPTH values in the regional veins obtained during selective venous sampling (Table). On further review, she had increased sestamibi uptake in the region of her left submandibular gland that was concordant with the results of her selective venous sampling. The patient's neck was reexplored through her previous cervical incision. Dissection high in the carotid sheath demonstrated a 0.8-g hypercellular parathyroid adenoma anterior to the carotid bifurcation. She was rendered normocalcemic.

Patient 3 was a 58-year-old woman with non-dialysis-dependent chronic renal insufficiency. Before her presentation, she had undergone 2 previous explorations elsewhere with resection of 3½ parathyroid glands for symptomatic secondary hyperparathyroidism. Her symptoms persisted and, at presentation, she had an elevated iPTH level of 957 pg/mL and calcium level of 9.7 mg/dL (2.4 mmol/L). Preoperative imaging included a sestamibi scan that was interpreted as nondiagnostic.

However, selective venous sampling indicated the presence of a high left cervical source of parathyroid hormone (Table), and rereview of the sestamibi imaging suggested that there was increased activity in the region of the left submandibular gland (Figure 4). Ultrasonographic examination of the neck was unrevealing. The patient's neck was subsequently reexplored through her previous cervical incision by means of a lateral approach. After developing the plane between the strap muscles and the sternocleidomastoid muscle, the carotid sheath was explored to the angle of the jaw and a 1.9-cm adenoma was identified lateral to the left internal carotid artery. Postoperatively, the patient's secondary hyperparathyroidism was resolved. In retrospect, the pattern of sestamibi radioactivity was that of an adenoma next to the left submandibular gland.

Endocrine surgeons are in a unique position to refine and improve the interpretation of sestamibi parathyroid images. The surgeon's understanding of the potential sites for parathyroid adenomas—especially relative to the thyroid as seen on the sestamibi images—can greatly improve the interpretation of the scan. Consequently, the surgeon is often able to point out sites of radioactivity that should be examined with extra care. The surgeon's view will be validated by retrospectively comparing the location of an excised adenoma with subtle variations in sestamibi retention. This series further demonstrates the importance of correlating selective venous sampling results with sestamibi imaging to enhance reoperative parathyroid surgery.

As an example of this process, we identified 3 patients with hyperparathyroidism resulting from an undescended left inferior parathyroid adenoma. In each case, a sestamibi scan had been performed as part of a localization protocol to aid in operative planning. These scans were initially interpreted as a “negative” or “nondiagnostic,” as there was no focal uptake in the usual parathyroid locations. However, with additional scrutiny, each scan actually demonstrated the finding of asymmetry between the 2 submandibular salivary glands. A SPECT

Figure 2. Early (A) and delayed (B) images obtained with patient 1 in the left anterior oblique position. Arrow indicates asymmetric activity in the region of the left submandibular salivary gland. This finding persists on the delayed view.

### Intact Parathyroid Hormone (iPTH) Values Obtained During Selective Venous Sampling Studies

<table>
<thead>
<tr>
<th>Anatomic Location</th>
<th>iPTH, pg/mL</th>
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<tbody>
<tr>
<td>Patient 1</td>
<td>Patient 2</td>
</tr>
<tr>
<td>Right high internal jugular vein</td>
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</tr>
<tr>
<td>Right mid-internal jugular vein</td>
<td>317</td>
</tr>
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<td>Right low internal jugular vein</td>
<td>301</td>
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reconstruction suggested that radioactivity accumulation represented both the left submandibular gland and a separate entity inferior and posteromedial to the gland. This conclusion was corroborated by the results of the selective venous sampling in 3 patients and cervical ultrasound in 1 patient. Given the evidence provided herein, additional postoperative sestamibi studies were not necessary to demonstrate the absence of the asymmetric sestamibi avidity and would not have been clinically indicated in these cured patients.

Given the recent interest in targeted parathyroidectomy based on preoperative imaging, surgeons must strive to improve the sensitivity and specificity of sestamibi scanning. Although previously considered controversial, preoperative localization is now frequently used to facilitate a limited, unilateral neck exploration, thereby reducing cost and patient morbidity in patients with primary disease. On the basis of a carefully constructed decision analytic model, Fahy and colleagues suggested that preoperative localization of parathyroid adenomas appears to represent a cost-effective strategy for treating primary and recurrent hyperparathyroidism. In specific, the cost derived from the model for preoperative imaging coupled with intraoperative parathy-

Figure 3. Early (A) and delayed (B) images obtained with patient 2 in the anteroposterior position. Again, there is asymmetric activity in the region of the left submandibular salivary gland (see black arrow on early image). This finding is more evident on the early view and is absent by the time the delayed view was obtained.

Figure 4. Early (A) and delayed (B) images obtained with patient 3 in the anteroposterior position. Note the asymmetric activity in the region of the left submandibular salivary gland. This finding is more evident on the delayed view (black arrow).
roid monitoring and unilateral neck exploration (performed on an outpatient basis) was found to be less than a 4-gland exploration, particularly when the cost of failed exploration was considered.

The undescended parathyroid adenoma is particularly difficult to identify preoperatively, potentially leading to failure of the minimally invasive approach. Autopsy studies suggest that, although only 2% of glands are ectopically located (eg, high in the carotid sheath or in the chest), they accounted for 17 (7%) of 255 cases of persistent hyperparathyroidism treated at the National Institutes of Health, Bethesda, Md. Reports suggest that sestamibi studies have the highest true-positive rates and lowest false-negative rates among the various imaging modalities. Sestamibi is concentrated in thyroid, parathyroid, and salivary gland tissue, and the radionuclide generally washes out of thyroid tissue more rapidly than from parathyroid adenomas, permitting identification of parathyroid adenomas on delayed images. This technique, combined with SPECT reconstruction, locates 50% to 95% of parathyroid adenomas. The use of SPECT provides 3-dimensional imaging often crucial when an undescended parathyroid adenoma is identified behind the submandibular salivary gland, as was demonstrated in our patients and the single previous report of this finding.

This study suggests that the best interpretation of preoperative sestamibi scans will require the ability and willingness to comment on subtle findings even if these findings are nondiagnostic (such as asymmetry or nonpersistent activity). In addition, the attending surgeon should review scans in collaboration with the interpreting nuclear medicine specialist before reexploration is planned and undertaken. This is especially important for scans in which findings are potentially nondiagnostic or inconclusive. Finally, the loop is closed when the surgeon and nuclear medicine specialist again review the scan together with the benefit of postoperative knowledge of the exact location of the adenoma. With adherence to these principles, the missions of both patient care (present and future) and physician education are enhanced.

CONCLUSIONS

Ectopic undescended inferior parathyroid adenomas represent an unusual cause of persistent hyperparathyroidism overall but are a not uncommon cause of persistent hyperparathyroidism after operation. Preoperative sestamibi scanning combined with SPECT can localize these lesions if careful attention is paid to the contour and symmetry of the activity in the region of the submandibular salivary glands. We report this finding to alert endocrine surgeons who use sestamibi scanning in the preoperative and primary setting. If the interpretation is equivocal, corroborating evidence may be obtained with selective venous sampling for iPTH measurements.

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Corresponding author: Paul G. Gauger, MD, Department of Surgery, University of Michigan Hospital, Taubman Center, 1500 E Medical Center Dr, TC2920H, Ann Arbor, MI 48019 (e-mail: pgauger@umich.edu).

REFERENCES