Chapter 8
Ectopic Parathyroid Adenoma

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Case Presentation

A 50-year-old female was diagnosed with primary hyperparathyroidism (PHPT) based on a laboratory evaluation obtained during evaluation for recurrent nephrolithiasis. She described a history that included passing greater than 300 calcium oxalate kidney stones over the course of the past 20 years despite medical therapy with hydrochlorothiazide and potassium citrate, as well as maintenance of a low oxalate diet. Laboratory evaluation over time had revealed a progressive mild increase in serum calcium and parathyroid hormone (PTH) levels. Her most recent values are listed in Table 8.1. ^{99m}Tc-sestamibi/iodine-123 scintigraphy demonstrated a discordant focus of activity in the superior mediastinum consistent with an ectopic parathyroid adenoma, with no evidence for a thyroidal location (Fig. 8.1).

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Assessment and Diagnosis

The incidence of ectopic parathyroid glands in patients with PHPT has been reported to range from 5 % to 20 % [1–5]. Ectopic parathyroid glands can significantly impact morbidity and clinical outcomes primarily due to failure during parathyroid exploration and subsequent requirement for reoperation. It has been estimated that 24–53 % of cases of reoperation for persistent or recurrent PHPT are due to the ectopic location of the diseased gland(s) [2, 6, 7].

The clinical and biochemical features of orthotopic versus ectopic parathyroid adenomas have been evaluated in several cohorts. On average, ectopic parathyroid adenomas are both usually significantly larger and associated with higher serum calcium levels [1, 4, 8]. In one cohort, it was also noted that radiographic evidence of osteitis fibrosa cystica was more frequent in patients with ectopic parathyroid adenomas [1]. There do not appear to be other significant differences in terms of patient characteristics (age, gender) or biochemical (serum phosphorus and PTH levels), clinical (presence of nephrolithiasis, hypertension, pancreatitis, and osteoporosis), or histopathologic features (adenoma, hyperplasia, or carcinoma) in subjects with orthotopic versus ectopic parathyroid adenomas.

The parathyroid glands originate from the third and fourth pharyngeal pouches, with differentiation beginning during the fifth and sixth weeks of development. Whereas parathyroid

Table 8.1 Patient's most recent laboratory data

Analyte	Results	Reference range
Calcium	10.5	8.9–10.1 mg/dL
Parathyroid hormone (PTH)	68	15–65 pg/mL
Creatinine	0.8	0.6–1.1 mg/dL
25-hydroxyvitamin D	31	20–50 ng/mL
24-h urine calcium excretion	439	25–300 mg/24 h

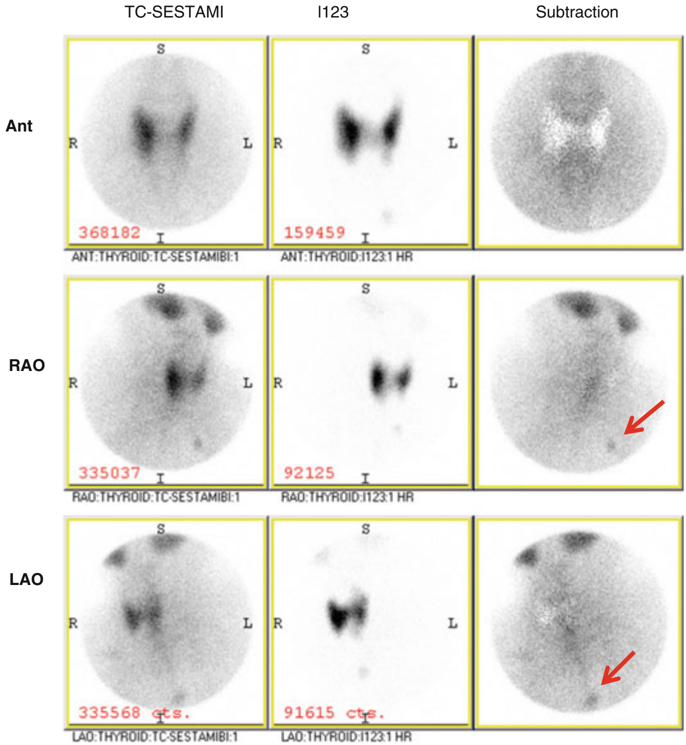

Fig. 8.1 ^{99m}Tc-sestamibi (first column); iodine-123 (second column) and subtraction (third column) scintigraphy images showing a discordant focus of activity in the superior mediastinum consistent with an ectopic parathyroid adenoma. *Ant* anterior, *RAO* right anterior oblique, *LAO* left anterior oblique

tissue from the fourth pharyngeal pouch eventually migrates to give rise to the superior parathyroid glands, parathyroid tissue from the third pharyngeal pouch migrates caudally before arresting at the level of the thyroid to become the inferior parathyroid glands. Due to their longer migration path, the inferior parathyroid glands have a greater probability of becoming ectopic [9]. Notably, inferior glands commonly have associated thymic tissue due to the common third pharyngeal pouch embryonic origin of the thymus and inferior parathyroid glands. The most common locations for ectopic inferior parathyroid glands are intrathymic, the anterosuperior mediastinum, intrathyroidal, associated with the thyrothymic ligament, or in the submandibular area (Fig. 8.2). Less commonly, ectopic parathyroid glands derived from the inferior parathyroid can be found in the aortopulmonary window or associated with the pericardium, hypopharynx, nasopharynx, vagus nerve sheath, or posterior cervical triangle [1, 3–5, 10–12]. Superior parathyroid glands, when ectopic, are most commonly localized to the tracheoesophageal groove, retroesophageal space, posterosuperior mediastinum, intrathyroidal, carotid sheath, or paraesophageal space. One potential explanation for the ectopy of superior glands is that with disease development the parathyroid gland becomes larger and heavier, leading to vertical displacement by gravity [1, 3, 4, 10, 13].

Surgical and autopsy data demonstrate that most ectopic parathyroid glands originate from inferior glands (62 % vs. 38 % from superior glands) [4]. Most are accessible via a cervical incision due to tracheoesophageal groove (28–43 %), intrathymic (24–31 %), or intrathyroidal (7–22 %) locations. The remainder are most frequently mediastinal (14–26 %) or located in the carotid sheath (7–9 %), aortopulmonary window, or submaxillary region [1, 2, 4]. In a cohort of mediastinal ectopic parathyroid glands performed at the Mayo Clinic, 45 % of patients required open thoracotomy or mediastinotomy, while 55 % of patients underwent a minimally invasive approach (such as video-assisted thoracoscopy, manubrium split, or transcervical approach) [18]. No significant difference in outcomes over a mean 3-year follow-up period was seen between subjects who underwent open versus minimally invasive surgical approaches.

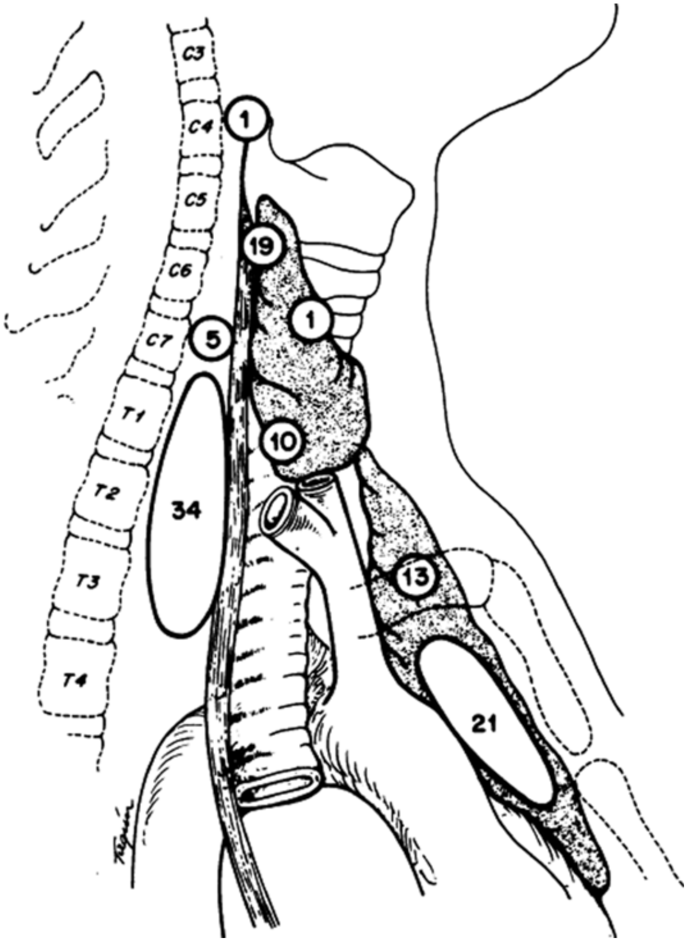

Fig. 8.2 Anatomic localization of 104 ectopic parathyroid glands. Superior posterior mediastinum ($n=34$); anterior mediastinum ($n=21$); dorsum of the upper ($n=19$) and lower ($n=10$) poles of the thyroid; within the thymic tongue ($n=13$); retroesophageal ($n=5$); at the angle of the jaw ($n=1$); and intrathyroidal ($n=1$) (Reprinted from Wang et al. [10] with permission)

Most surgeries performed for ectopic parathyroid gland resection are reoperations due to recurrent or persistent hyperparathyroidism disease after initial surgery. Reoperations typically occur in referral tertiary care centers. Due to the complexity of these operations and the potential for significant scar tissue present after initial extended parathyroid gland explorations, identifying an experienced parathyroid surgeon can be as essential as detecting the diseased parathyroid gland.

In the absence of preoperative localization, the surgeon typically carefully inspects all four orthotopic parathyroid glands in order to detect any abnormal gland. When less than four glands are found, it is recommended that the surgeon carefully inspects likely ectopic locations accessible via a cervical approach including the tracheoesophageal groove, thymus, ipsilateral thyroid, and upper cervical region [13].

Multiple imaging modalities are available for parathyroid adenoma localization and are associated with varying degrees of localization accuracy. Most reported cohorts, although limited in terms of sample sizes, suggest that patients are more likely to undergo successful surgical resection if localizing techniques are employed preoperatively [6]. Furthermore, preoperative localization for identification of ectopic glands can alter the operative approach depending on the ectopic gland location (i.e., substernal, aortopulmonary, or submandibular locations) [4, 10, 14].

Protocols for imaging prior to initial surgery are center specific and are typically based on local data in large referral tertiary care centers. However, prior to reoperation for persistent or recurrent PHPT, most surgical centers perform some combination of preoperative and/or intraoperative localization techniques (including intraoperative PTH measurements, intraoperative gamma probe, or a frozen section of the removed surgical specimen) [7, 15].

^{99m}Tc-sestamibi scintigraphy has the highest sensitivity of localizing a single adenoma (90 %). The sensitivity, however, is decreased for double adenomas (30–73 %) and hyperplasia (45–60 %). Combining ^{99m}Tc-sestamibi scintigraphy with ^{123}I or

^{99m}Tc/^{99m}Tc-sestamibi subtraction eliminates potential false-positive results from thyroid nodules [13]. In one series, the positive predictive value for the detection of ectopic glands was 100 % compared to 98 % for parathyroid glands in normal anatomic locations [4]. On rare occasions, false negatives may result from ectopic parathyroid adenomas located at the carotid bifurcation as this location can sometimes be mistaken for physiological activity of the ipsilateral submandibular gland [16]. For completeness, scintigraphy should extend from the base of the jaw to the base of the heart in order to detect any ectopic glands along the full embryologic migratory course of the inferior glands [17].

Combination with another imaging technique can at times improve accuracy of preoperative localization. As example, intrathymic and aortopulmonary adenomas may have similar mediastinal activity on ^{99m}Tc-sestamibi scintigraphy. Oblique or lateral images might help in differentiating these two locations. Single-photon emission computed tomography (SPECT) allows for determination of depth relative to the thyroid gland [17], with Doppman et al. suggesting that SPECT imaging be considered whenever ^{99m}Tc-sestamibi scintigraphy demonstrates a deep mediastinal adenoma [12]. Alternatively, in some cases additional computed tomography (CT) or magnetic resonance imaging (MRI) may provide additional valuable information for the surgeon. Both CT and MRI have demonstrated great ability to detect ectopic parathyroid glands. Importantly, although CT is more readily available, it may have comparatively lower definition within the thyroid area [13].

Management

In addition to the parathyroid scan with ^{99m}Tc-sestamibi/iodine-123 scintigraphy, the patient had SPECT/CT images of the neck and chest which confirmed the ectopic location of her parathyroid adenoma. In conjunction with an experienced endocrine surgeon, a thoracic surgery team with significant previous experience in minimally invasive ectopic mediastinal parathyroid gland excision [18] evaluated the patient. After consultation, both surgical teams agreed that a left thoracoscopic approach was indicated. The endocrine surgeon was present during the surgery and assisted in intraoperative identification of the ectopic gland.

Outcome

The patient underwent resection of the mediastinal ectopic parathyroid adenoma identified on preoperative imaging via a left thoracoscopic approach. Pathology confirmed a 430-mg parathyroid adenoma. Intraoperative PTH measurements confirmed cure after the resection of the adenoma based on a decline from a baseline value of 74 to 24 pg/mL at 20 min following resection. Postoperative biochemical testing revealed serum calcium 9.2 mg/dL, ionized calcium 5.17 mg/dL (nl, 4.80–5.70 mg/dL), and PTH 55 pg/mL.

Clinical Pearls/Pitfalls

- Referral to a tertiary medical center with an experienced parathyroid surgeon and a radiology service with expertise in parathyroid imaging is important in patients in whom an ectopic parathyroid adenoma is suspected.
- Ectopic adenomas are usually significantly larger and associated with higher serum calcium levels compared to orthotopic adenomas.

- When less than four glands are identified intraoperatively, it is recommended that the surgeon carefully inspects common ectopic locations accessible via a cervical approach.
- Prior to reoperation for persistent or recurrent PHPT, most referral tertiary care centers perform some combination of preoperative and/or intraoperative localization techniques.
- Extending scintigraphy from the base of the jaw to the base of the heart allows for detection of ectopic inferior glands.
- Combining scintigraphy with another imaging technique, such as SPECT, CT, or MRI, can at times improve accuracy of preoperative localization.

Conflicts of Interest All authors state that they have no conflicts of interest.

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