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Narrative literature review of ectopic parathyroid adenoma in the submandibular region following a case detected by ^{18}F-FCH PET/CT

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Abstract

Ectopic parathyroid glands pose a significant challenge in the diagnosis and management of primary hyperparathyroidism, particularly when minimally invasive parathyroidectomy is planned, because its success depends heavily on accurate preoperative localization. Ectopic parathyroid adenomas in the submandibular region are exceptionally rare, and their surgical management may require conversion to bilateral open exploration or subsequent reoperation because of persistent disease.

Prompted by a complex clinical case, this narrative review examines the current literature on ectopic submandibular parathyroid adenomas, with particular emphasis on diagnostic strategies, imaging modalities, and surgical considerations. The findings underscore the critical importance of precise preoperative localization for successful targeted resection, even in challenging ectopic presentations.

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INTRODUCTION

Primary hyperparathyroidism (PHPT) is caused by increased activity of the parathyroid glands resulting in excessive secretion of parathyroid hormone (PTH). Most cases are caused by a single adenoma (85 %), of which 5 %-20 % are ectopic (1-4), and, less frequently, by hyperplasia of all 4 glands (10 %-15 %) (2,5-7). PHPT has an approximate prevalence of 1 % in the general population, with a female-to-male ratio of 3-4:1, and typically affects middle-aged women between 40 and 60 years of age (3,6-8). It is the third most common endocrine disorder after diabetes *mellitus* and thyroid disease (2,3,5,7).

The diagnosis of PHPT is biochemical and is often established incidentally after hypercalcemia is detected on repeated laboratory testing, regardless of the presence of clinical symptoms suggestive of the disease. Simultaneous elevation of serum calcium and PTH levels is required for diagnosis.

The curative treatment for PHPT is surgical removal of the affected parathyroid gland or glands. Once PHPT has been diagnosed, surgery is considered in patients who meet the criteria established by European and US guidelines (9-11). Preoperative imaging to localize hyperfunctioning parathyroid glands is indicated only when surgical treatment is planned.

Traditionally, surgery consisted of standard bilateral cervical exploration (BCE), with the aim of identifying all 4 parathyroid glands. Surgical management has now evolved toward a more targeted approach, namely minimally invasive parathyroidectomy (MIP), for which precise preoperative localization plays a fundamental role. MIP reduces pain and complications, shortens operative time and hospital stay, lowers healthcare costs, and provides better cosmetic outcomes (2,6).

The combination of ^{99m}Tc-sestamibi scintigraphy and ultrasonography is currently considered a standard first-line approach for localization of parathyroid adenomas (6). However, when findings are negative, uncertain, or discordant, guidelines recommend additional imaging techniques according to local availability, including single-photon emission computed tomography/computed tomography (SPECT/CT), 4-dimensional computed tomography (4D-CT), or magnetic resonance imaging (4D-MRI) (9,10). More recently, PET/CT with ^{18}F-fluorocholine (^{18}F-FCH PET/CT) has been increasingly used for localization of parathyroid adenomas.

Ectopic localization of a parathyroid adenoma in the submandibular triangle is uncommon and represents a diagnostic and surgical challenge (12). Despite its complexity, adequate preoperative radiologic localization and intraoperative tools such as intraoperative PTH (ioPTH) monitoring can enable effective MIP even in these atypical ectopic cases. We present the case of a patient with persistent PHPT after previous BCE, without postoperative normalization of calcium or PTH levels, in whom an occult ectopic adenoma was suspected.

MATERIAL AND METHODS

STUDY DESIGN

We conducted a narrative literature review to analyze the available scientific evidence on ectopic parathyroid adenomas in the submandibular region.

INFORMATION SOURCES

The literature search was performed in PubMed/MEDLINE. Articles published up to July 2025 were included.

SELECTION CRITERIA

Included: Original articles, reviews, meta-analyses, and case reports.

Excluded: Articles for which the full text was unavailable and studies not relevant to the topic.

SEARCH STRATEGY

The following MeSH terms and keywords were used: primary hyperparathyroidism; submandibular ectopic parathyroid adenoma; ultrasound; ^{99m}Tc-sestamibi scintigraphy; SPECT/CT; and ^{18}F-fluorocholine PET/CT. The Boolean operators AND and OR were used to combine search terms.

DATA EXTRACTION

The following data were collected from each article:
- Article title, first author, city, year of publication, and reference.
- Study design and sample size.
- Main results relevant to the topic, including number of surgical procedures, preoperative imaging, surgical technique, time to case resolution, complications, and conclusions.

DATA SYNTHESIS

The extracted data were organized descriptively in tabular form to summarize and compare the findings of the different studies (Table I).

Table I. Literature review of ectopic parathyroid adenomas in the submandibular region

Title	Author, year, city/country	*n*	Design	Imaging	No. of surgical procedures/ technique	Location	Complications	Time to resolution	Conclusion
SPECT and subtraction imaging of an ectopic parathyroid adenoma (23)	LS Serchuk, 1997, United States	1 (1 submandibular)	Case report	^{99m}Tc-sestamibi + SPECT and subtraction imaging	2 (BCE)	In relation to the right submandibular salivary gland	-	-	SPECT localized the ectopic parathyroid adenoma in relation to the right submandibular salivary gland, whereas subtraction imaging confirmed that the focus represented a parathyroid lesion rather than an anatomical variant of a normal salivary gland
Localization of abnormal parathyroid tissue with use of technetium-99m-sestamibi (14)	VG Calcutt, 1997, United States	24 (1 submandibular)	Case series	^{99m}Tc-sestamibi	3 (BCE)	Medial to the right carotid artery, below the angle of the mandible	No	-	Precise localization of an adenoma facilitates surgical exploration. ^{99m}Tc-sestamibi has become a preferred noninvasive method for localizing ectopic parathyroid glands
Appearance of ectopic undescended inferior parathyroid adenomas on technetium-99m sestamibi scintigraphy: a lesson from reoperative parathyroidectomy (6)	D Axelrod, 2003, United States	3 (3 submandibular)	Case series	^{99m}Tc-sestamibi	3 (BCE + thymectomy + subtotal thyroidectomy)	In the left carotid sheath, inferior to the angle of the mandible	-	-	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 and facilitate selective surgery
65-year-old female patient with persistent hypercalcemia (21)	Wiedmann, 2007, Germany	1 (1 submandibular)	Case report	^{99m}Tc-sestamibi + SPECT + CT + US	2 (BCE + thyroidectomy)	Left submandibular region	Transient hypocalcemia	—	If an adenoma is not identified during exploratory surgery, an ectopic location should be considered; surgery may be discontinued and further localization studies performed before reoperation
Para-hyoid ectopic parathyroid adenoma localized by ^{99m}Tc-MIBI SPECT (22)	Rajagopalan, 2008, United States	1 (1 submandibular)	Case report	^{99m}Tc-sestamibi + SPECT + CT + US	2 (BCE)	Posteroinferior parahyoid adenoma of the right submandibular gland	-	2 years	Attention should be paid to an uptake focus in the "submandibular tail," which may indicate an ectopic parathyroid adenoma in the submandibular region
Adenomas of cervical maldescended parathyroid glands: pearls and pitfalls (2)	James C Lee, 2012, Australia	5241 (1 submandibular)	Case series	^{99m}Tc-sestamibi + US	1 (MIP)	Submandibular triangle	-	-	High surgical success rates can be achieved with MIP when knowledge of embryology is combined with reliable preoperative localization
Ectopic undescended parathyroid adenoma-SPECT/CT avoids false-negative interpretation on ^{99m}Tc-MIBI dual-phase scintigraphy (4)	S Mahajan, 2018, United States	1 (1 submandibular)	Case report	^{99m}Tc-sestamibi + SPECT/CT	-	Ectopic adenoma inferior to the left submandibular gland	-	-	Ectopic adenomas adjacent to the submandibular gland may be overlooked on scintigraphy because of overlapping salivary gland activity. This case demonstrates the potential advantage of SPECT/CT over sestamibi scintigraphy alone

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Table I (cont). Literature review of ectopic parathyroid adenomas in the submandibular region

Title	Author, year, city/country	*n*	Design	Imaging	No. of surgical procedures/ technique	Location	Complications	Time to resolution	Conclusion
Ectopic parathyroid adenoma in the submandibular region: a case report (24)	Y Kong, 2019, China	1 (1 submandibular)	Case report	^{99m}Tc-sestamibi + SPECT/CT	1 (MIP)	Posteromedial to the left submandibular gland	No	-	Ectopic parathyroid adenoma should be considered in the differential diagnosis of tumors of the submandibular region
Acute hyperparathyroid crisis: ectopic submandibular parathyroid gland the culprit (13)	M Unais, 2020, India	1 (1 submandibular)	Case report	US + CT	2 (MIP)	Right submandibular region	No	1 week	Precise localization of the adenoma is essential, particularly in life-threatening situations such as hyperparathyroid crisis. Imaging has limitations, and further surgical exploration may be necessary
Ectopic submandibular parathyroid adenoma by ^{99m}Tc-sestamibi SPECT/CT localization (1)	Fung Him Ng, 2020, China	1 (1 submandibular)	Case report	^{99m}Tc-sestamibi + SPECT/CT	-	Inferior to the right submandibular gland	-	-	Ectopic adenomas require a multimodal approach to operative planning. SPECT/CT provides useful anatomical information
^{99m}Tc-MIBI SPECT/ CT-negative ectopic parathyroid adenoma in the submandibular region: a case report (18)	Y Lai, 2023, China	1 (1 submandibular)	Case report	^{99m}Tc-sestamibi + SPECT/ CT + US + ^{11}C-choline PET/CT	2 (BCE + right hemithyroidectomy)	Submandibular region, posterior to the right submandibular gland	No	6 years	Ectopic adenoma in the submandibular region is exceptionally rare. When conventional imaging is negative, clinical suspicion should be maintained, and ^{11}C-choline PET/CT may accurately localize the lesion and facilitate successful surgery
Submandibular ectopic parathyroid adenoma: a case report (26)	JA H Tawil, 2023, Colombia	1 (1 submandibular)	Case report	^{99m}Tc-sestamibi + SPECT/CT + US + ^{18}F-FCH PET/CT	1 (MIP)	Right submandibular region	No	6 months	Surgical management of PHPT reduces morbidity and mortality. Ectopic locations should be considered. ^{18}F-FCH PET/CT can precisely localize the adenoma and facilitate successful surgery
Multimodality evaluation of persistent hyperparathyroidism in a rare case of ectopic submandibular parathyroid adenoma (25)	Edamadaka, 2024, India	1 (1 submandibular)	Case report	^{99m}Tc-sestamibi + SPECT/CT + US + 4D-CT	1 (MIP)	Submandibular region	-	-	^{99m}Tc-MIBI SPECT/CT and 4D-CT may improve preoperative detection of parathyroid adenomas in rare ectopic locations, as illustrated by this case of persistent hyperparathyroidism
Management of primary hyperparathyroidism with rare localization of ectopic parathyroid adenoma (7)	Aboisheva, 2024, Russia	1 (1 submandibular)	Case report	^{99m}Tc-sestamibi + SPECT/CT + US + CT	Conservative therapy (high surgical risk)	Posterior to the internal jugular vein, adjacent to the right submandibular gland	No	10 years	Ectopic adenomas complicate topographic diagnosis and may require advanced imaging methods. Management should be individualized according to lesion location and patient comorbidities

4D-CT, four-dimensional computed tomography; BCE, bilateral cervical exploration; CT, computed tomography; ^{18}F-FCH, ^{18}F-fluorocholine; MIP, minimally invasive parathyroidectomy; PET, positron emission tomography; PHPT, primary hyperparathyroidism; SPECT, single-photon emission computed tomography; SPECT/CT, single-photon emission computed tomography/computed tomography; US, ultrasonography.

CASE REPORT

A 42-year-old White woman presented to her primary care physician with dizziness and generalized weakness of 3 days' duration. Her past medical history included hypertension treated with hydrochlorothiazide. Physical examination findings and vital signs were unremarkable. Laboratory testing revealed hypercalcemia, with a protein-corrected calcium level of 10.3 mg/dL.

Further evaluation showed phosphorus, 2.5 mg/dL; PTH, 156 pg/mL; vitamin D, 43 ng/mL; and thyroid-stimulating hormone, 1.6 µIU/mL. A 24-hour urine collection showed hypercalciuria (486 mg/24 h). The patient was referred to the Department of Endocrinology.

Targeted history taking confirmed symptoms compatible with PHPT, including arthralgia, asthenia, and dizziness. The patient had no history of pathological fractures but reported 2 episodes of nephrolithiasis 2 years earlier. Abdominal ultrasonography and radiography ruled out current nephrolithiasis. Bone densitometry showed lumbar and femoral *z*-scores within the normal range for her age and sex.

INVESTIGATIONS AND DIFFERENTIAL DIAGNOSIS

The patient's evaluation began after the incidental detection of hypercalcemia. The differential diagnosis included PHPT, malignancy-associated hypercalcemia, vitamin D intoxication, chronic kidney disease, medications such as thiazides and lithium, familial hypocalciuric hypercalcemia, and granulomatous diseases such as sarcoidosis and tuberculosis (11).

After correction of concomitant vitamin D deficiency with monthly calcifediol and discontinuation of hydrochlorothiazide, repeated laboratory testing showed persistent abnormalities: calcium, 10.4 mg/dL; PTH, 128 pg/mL; and urinary calcium, 594 mg/24 h. These findings confirmed PHPT after secondary causes had been excluded.

The patient met European and US criteria for surgery because of her age and persistent hypercalcemia (9-11). Surgical treatment was proposed and accepted. Initial imaging with cervical ultrasonography and ^{99m}Tc-sestamibi SPECT/CT was negative. Endoscopic ultrasonography identified a possible 4-mm left inferior parathyroid adenoma adjacent to the vascular bundle.

The patient underwent bilateral neck exploration. The left side was explored first without identification of a lesion. Exploration then proceeded to the right side, where a 2-cm nodule was excised and sent for histopathological examination. Intraoperative PTH monitoring showed no decrease (baseline PTH, 135 pg/mL; ioPTH, 165 pg/mL; percentage decrease, –1.85 %), prompting extended exploration of the retroesophageal, thymic, thyroid capsular, and vascular compartments without further findings. Because a mediastinal ectopic adenoma was suspected, the procedure was concluded. Postoperative calcium remained elevated at 10.7 mg/dL. Histopathological examination identified the excised tissue as a reactive lymph node.

The patient was followed for 4 years. Laboratory abnormalities persisted: calcium, 11.2 mg/dL; PTH, 197 pg/mL; and urinary calcium, 172 mg/24 h. Repeated imaging studies remained negative. During this period, the patient experienced a new and more severe episode of renal colic. Abdominal ultrasonography confirmed a 2-mm calculus in the lower calyceal group of the left kidney.

Given the need for definitive treatment, a newer preoperative imaging modality that had recently been introduced in parathyroid surgery, ^{18}F-FCH PET/CT, was performed. This study identified a hypermetabolic lesion measuring 6 × 6 × 14 mm at left cervical level IIA in the submandibular region, adjacent to the submandibular gland (Fig. 1).

In the clinical context of this patient, visualization of a hypermetabolic focus in the submandibular region suggested an ectopic parathyroid adenoma. The differential diagnosis included reactive lymphadenopathy, salivary gland tumors, and superior thyroid lesions. These alternatives were excluded by fine-needle aspiration and PTH measurement in the aspirate, supporting the diagnosis of an ectopic parathyroid adenoma.

TREATMENT

Revision surgery was performed. Intraoperatively, a brownish nodule located posterior and caudal to the left submandibular gland and corresponding to the imaging findings was excised. ioPTH monitoring showed a > 50 % decrease (baseline PTH, 225 pg/mL; ioPTH, 87.6 pg/mL). Histopathological examination confirmed a 17-mm, 0.7-g parathyroid adenoma.

OUTCOME AND FOLLOW-UP

At 2 years postoperatively, the patient remains under follow-up. Her clinical symptoms have improved, with no further episodes of nephrolithiasis. Calcium and urinary calcium levels are within the normal range (8.5 mg/dL and 138 mg/24 h, respectively).

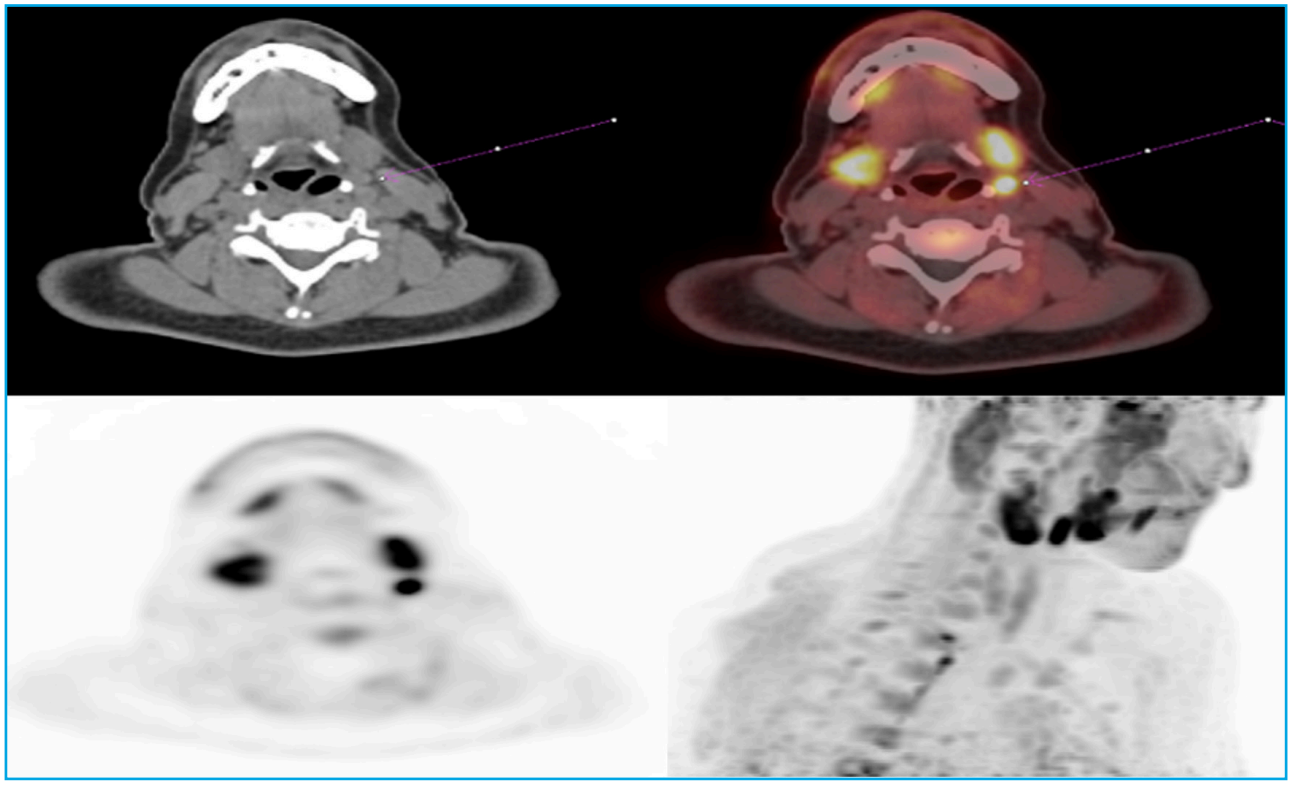

Figure 1. An elongated nodular lesion measuring approximately 6 mm × 6 mm × 14 mm (AP × T × CC) is identified in the left submandibular region at level IIA. The lesion is located posterior and inferior to the left submandibular gland, anterior to the vascular bundle, and medial to the sternocleidomastoid muscle. It appears hyperintense in the arterial phase, with intense ^{18}F-choline uptake, suggestive of an ectopic parathyroid adenoma. No other lesions showing radiotracer uptake are identified. Physiological tracer uptake is observed in the bone marrow, salivary glands, and thyroid gland. SUVmax values were 20.9 immediately after injection, 15.8 at 20 minutes, and 15.9 at 60 minutes.

DISCUSSION

The parathyroid glands usually consist of 4 small oval structures located on the posterior surface of the thyroid gland. However, their position may vary, making localization difficult in some patients, as occurred in the present case. Ectopic localization has been reported in up to 20 % of cases (2-4). The most frequent ectopic locations include the retroesophageal, thymic, carotid, mediastinal, and intrathyroidal regions, whereas the submandibular region is among the rarest sites (2,4,7,8).

This atypical high cervical or submandibular location (< 1 %) can be explained by abnormalities in embryological migration of the parathyroid glands. Such lesions are often referred to as high cervical or undescended parathyroid adenomas and may resemble lymph nodes or salivary gland lesions (2,4,12). Lee et al. reported 16 high cervical adenomas among 5241 patients (0.3 %), only 1 of which was located in the submandibular region. Fourteen occurred during primary parathyroidectomy and 2 were identified at reoperation. In this group, scintigraphy had a sensitivity of 67 %, and 9 patients required BCE (2).

Treatment of PHPT is surgical, and resection of the hyperfunctioning parathyroid gland or glands is curative. Reoperation is relatively common in patients with ectopic adenomas after failed initial surgery (2,13). Axelrod et al. reported 3 ectopic submandibular adenomas identified only during revision surgery (6). Calcutt et al. described a case requiring 3 surgical procedures before the submandibular adenoma was identified (14). Accurate preoperative localization is therefore crucial to minimize unnecessary surgical exploration. Aboisheva et al. reported the case of an 84-year-old woman who underwent years of conservative medical management without normalization of calcium levels because the pathological focus could not be identified (7).

Conventional imaging modalities, including scintigraphy and ultrasonography, have reported sensitivity and specificity rates of approximately 70 %-80 % for adenoma detection (3-5,15-18). In the 20 %-30 % of patients with negative findings, more advanced imaging techniques may be required. ^{18}F-FCH PET/CT combines functional and anatomical imaging and provides greater spatial resolution with shorter acqui-

sition times and potentially lower radiation exposure. Despite its greater cost and limited availability, it has shown promising diagnostic performance. A 2019 meta-analysis reported a sensitivity of 95 %, positive predictive value of 97 %, and detection rate of 91 % for ^{18}F-FCH PET/CT (19), potentially avoiding unnecessary bilateral exploration in 75 %-87 % of cases (20).

The present case illustrates a rare ectopic submandibular adenoma diagnosed after years of persistent PHPT and unsuccessful surgery. Conventional imaging was nondiagnostic, whereas ^{18}F-FCH PET/CT provided precise localization and enabled curative surgery.

Few cases of parathyroid adenoma in the submandibular region have been published. Our literature review identified 14 articles indexed in PubMed, the earliest dating from 1997 (Table I). In most reported cases, the adenoma was detected using conventional imaging or SPECT/CT (1,4,21-26). Only 2 published cases described identification of a submandibular adenoma using PET/CT: 1 with an ^{11}C-choline tracer (18) and another with ^{18}F-choline (26). We report an additional case of a submandibular parathyroid adenoma localized using ^{18}F-FCH PET/CT after neither ^{99m}Tc-sestamibi scintigraphy with SPECT/CT nor cervical ultrasonography was able to detect the lesion.

Identification of an ectopic submandibular adenoma represents an exceptionally uncommon anatomical presentation and can pose a substantial challenge for the head and neck surgeon. Many of these patients have already undergone unsuccessful bilateral exploratory surgery and have persistent hyperparathyroidism, requiring revision surgery and thereby increasing the risk of postoperative complications. More accurate imaging modalities are therefore needed for preoperative localization to enable targeted resection, even in atypical ectopic cases such as the present one.

The use of ^{18}F-FCH PET/CT for preoperative localization in the surgical management of PHPT represents a significant advance in patient safety and clinical care. Its greater sensitivity and diagnostic accuracy allow more targeted and less invasive surgical planning. This may result in shorter operative times, a lower risk of complications such as recurrent laryngeal nerve injury and hypocalcemia, and faster recovery. Moreover, by increasing the likelihood of successful initial surgery, it may reduce the need for reoperation and thereby improve clinical outcomes and patients' quality of life.

CONCLUSIONS

The present case emphasizes the importance of surgical management of PHPT to reduce associated morbidity and potential complications. Rigorous clinical, biochemical, and radiological correlation is essential, together with the surgeon's awareness of the different embryological migration patterns of the parathyroid glands and their possible anatomical variants. This case also highlights the value of advanced preoperative imaging techniques in optimizing surgical outcomes, particularly in the context of minimally invasive approaches. ^{18}F-FCH PET/CT is a promising modality for preoperative localization of ectopic parathyroid adenomas. In the present case, it enabled accurate localization and curative surgical treatment after conventional imaging modalities had failed.

Finally, multidisciplinary clinical committees bringing together specialists from different fields, including endocrinology, otorhinolaryngology, radiology, and nuclear medicine, are important for the discussion and management of complex clinical cases.

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