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Recurrent Hyperparathyroidis Revealing Parathyromatosis: a Case Report

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ABSTRACT:

Introduction: Parathyromatosis is an extremely rare cause of recurrent or persistent primary hyperparathyroidism (PHPT), usually resulting from intraoperative seeding of parathyroid tissue following capsular rupture drecurruring surgery. Its diagnosis is difficult and may mimic parathyroid carcinoma.

Case Report: We report the case of a 50-year-old woman with recurrent PHPT after three parathyroid surgeries. The first operation in 2012 for a right inferior parathyroid adenoma achieved temporary remission. Two further recurrences occurred in 2017 and 2022, each treated surgically, but postoperative hypercalcemia and elevated parathyroid hormone (PTH) persisted. Cervical ultrasound and 18F-fluorocholine PET/CT revealed multiple small hypermetabolic nodules scattered in the right neck region, consistent with secondary parathyromatosis. Given the patient's refusal of further surgery, medical treatment with the calcimimetic cinacalcet was initiated, allowing long-term biochemical control at a dose of 120 mg/day.

Conclusion: Parathyromatosis should be considered in any patient with multiple recurrences of PHPT after parathyroidectomy. High-performance imaging, especially 18F-fluorocholine PET/CT, is essential for localization. Careful handling of parathyroid glands during surgery is crucial to prevent this rare but challenging complication. While surgery remains the treatment of choice, cinacalcet can represent an effective alternative for non-surgical candidates.

Keywords: Parathyromatosis; Recurrent hyperparathyroidism; Persistent hyperparathyroidism; 18F-fluorocholine PET/CT; Parathyroid carcinoma; Cinacalcet; Calcimimetic; Parathyroid surgery

INTRODUCTION:

Surgery remains the only curative treatment for primary hyperparathyroidism (PHPT), with a high success rate due to the development of advanced imaging techniques and intraoperative parathyroid hormone (PTH) monitoring [1]. However, 2.5% to 5% of patients will require reoperation due to the occurrence of persistent hyperparathyroidism, defined as the persistence or recurrence of hypercalcemia within six months after surgery, or recurrent hyperparathyroidism, characterized by the reappearance of PHPT more than six months after an initially curative parathyroidectomy [2].

Parathyromatosis is considered to be a rare cause of persistent or recurrent PHPT [3]. It is defined as the presence of multiple small nodules of hyperplastic and hyperfunctioning parathyroid tissue scattered

within the soft tissues of the neck and / or upper mediastinum. It is most often of iatrogenic origin, resulting from capsular rupture and dissemination of parathyroid cells during surgery, although rarely it may arise de novo [4]. Preoperative diagnosis is difficult and poses a major differential diagnostic challenge, especially with parathyroid carcinoma [5]. Management of this challenging condition is based on en bloc surgical resection of the parathyromatosis foci [4]. In case of failure or contraindication to surgery, medical treatment, mainly with calcimimetics, is indicated [6].

We report the case of a patient with PHPT who underwent three surgeries for recurrence and then persistence of hypercalcemia. A thorough imaging workup led to the diagnosis of parathyromatosis, which was subsequently controlled with medical treatment using calcimimetics. Through this case, we aim to highlight the diagnostic challenges and therapeutic strategies specific to this exceptional entity.

CASE REPORT:

Patient Background:

A 50-year-old woman was hospitalized in the Endocrinology Department at Hassan II University Hospital in Fez in 2016 for the evaluation and management of recurrent hyperparathyroidism. The medical history revealed renal stones treated by extracorporeal lithotripsy and JJ stent placement, with no chronic kidney disease, no specific medications, and no family history of multiple endocrine neoplasia (MEN) or familial hyperparathyroidism.

First Episode of Primary Hyperparathyroidism and Initial Surgery (2012):

The initial surgical indication in 2012 was prompted by severe hypercalcemia (4,74 mmol/l - 19 mg/dL), resulting from primary hyperparathyroidism caused by a large right inferior parathyroid adenoma (6×5×3 cm). The malignant hypercalcemia required four hemodialysis sessions and treatment with zoledronic acid, followed by parathyroid adenomectomy and right isthmo-lobectomy. Histology confirmed an adenoma and ruled out parathyroid carcinoma.

First Recurrence and reoperation (2016-2017):

Clinical and biochemical outcomes were favorable, with resolution of symptoms and normalization of calcium and PTH levels until 2016, when the patient presented with chronic fatigue and bone pain. Laboratory results revealed hypercalcemia at 2,96 mmol/l (11,9 mg/dL), hypophosphatemia at 0,64 mmol/l (2 mg/dL), and elevated PTH at 22,58 pmol/l (213 pg/mL) (2.66× the upper normal limit), confirming recurrent hyperparathyroidism.

Localization work-up, consisting of cervical MRI and MIBI scintigraphy, identified a right parathyroid nodule measuring 13×9 mm, along with thyroid nodules in the remaining lobe. Genetic analysis to investigate a syndromic cause could not be performed due to lack of availability. Assessment of PHPT-related complications showed hypercalciuria at 496 mg/day and kidney stones without bone complications.

A first reoperation was performed in 2017, consisting of total thyroidectomy and right unilateral parathyroidectomy. Histopathology confirmed a right parathyroid adenoma (1.9×1 cm) with benign thyroid hyperplasia.

Second Recurrence and Reoperation (2022):

The patient remained in complete remission until 2022, when similar symptoms reappeared. Laboratory findings confirmed recurrent PHPT with calcium at 3,26 mmol/l(13,1 mg/dL), phosphorus at 0,70 mmol/l (2,2 mg/dL), and PTH at 41,78 pmol/l (394 pg/mL) (5.8× upper normal limit). Multimodal imaging (ultrasound, cervico-thoracic CT scan, and MIBI scintigraphy) revealed a right- parathyroid

nodule at the base of the neck measuring 17×15 mm. Work-up for PHPT complications showed worsening hypercalciuria at 23,38 mmol/day (725 mg/day), moderate renal insufficiency with an eGFR of 56 ml/min, and dilation of the ureteropelvicalyceal system due to urolithiasis, with no associated cardiac or bone involvement.

A second reoperation was performed, with resection of the parathyroid adenoma. Histology confirmed the diagnosis, showing no atypia, mitoses, or invasion, and a thin capsule.

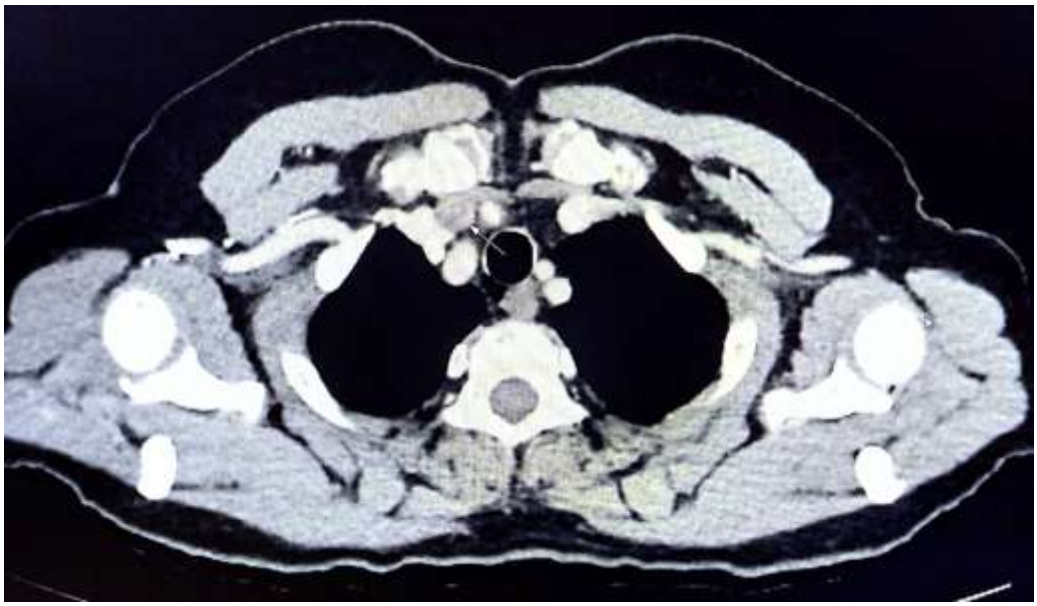


Figure 1 : CT scan image of the patient showing a right paratracheal parathyroid nodule (arrow) (performed at Hassan II University Hospital, Fez, Morocco)

Third failure of surgery with persistence of disease and work up (2022-2023):

Seven days postoperatively, persistent hyperparathyroidism was noted, with calcium at 126 mg/L and PTH at 182 pg/mL (3 × upper normal limit). A new localization work-up was performed. Cervical ultrasound identified multiple well-defined, homogenous, hypoechoic, and hypervascular nodules suggestive of parathyroid tissue in the right lateral neck:

- One in the right thyroid bed measuring 0.26 cm^2,
- Two anterior subfascial nodules adjacent to the right sternocleidomastoid muscle (0.11 cm^2 and 0.30 cm^2),
- One deep prevertebral, lateral to the esophagus, measuring 0.14 cm^2,
- One anterior subfascial, right-lateralized nodule measuring 0.4 cm^2.

These nodules appeared hypermetabolic on 18F-Choline PET-CT, consistent with parathyroid adenomas, with no evidence of ectopic parathyroid tissue.The diagnosis of secondary parathyromatosis was thus made.

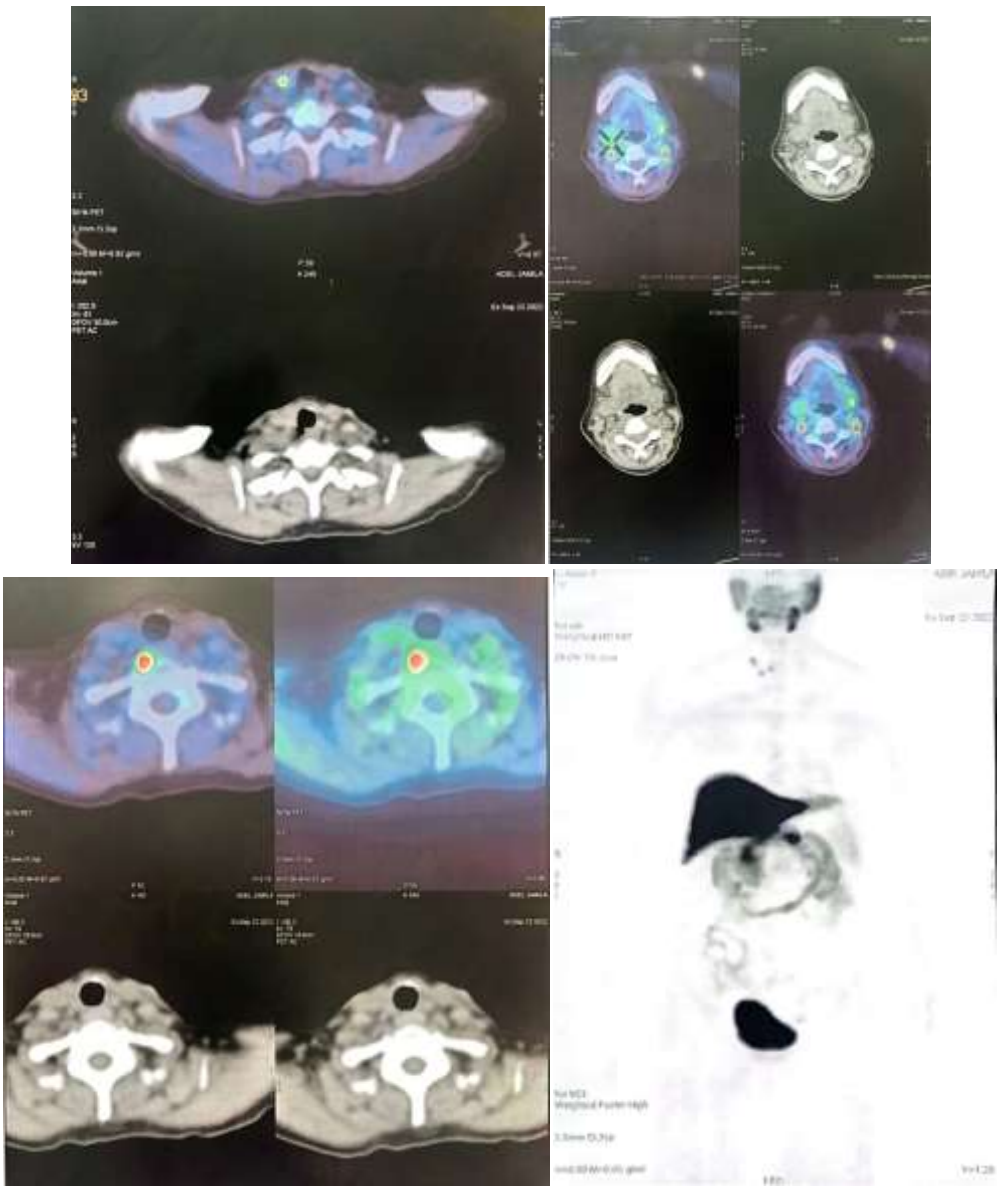
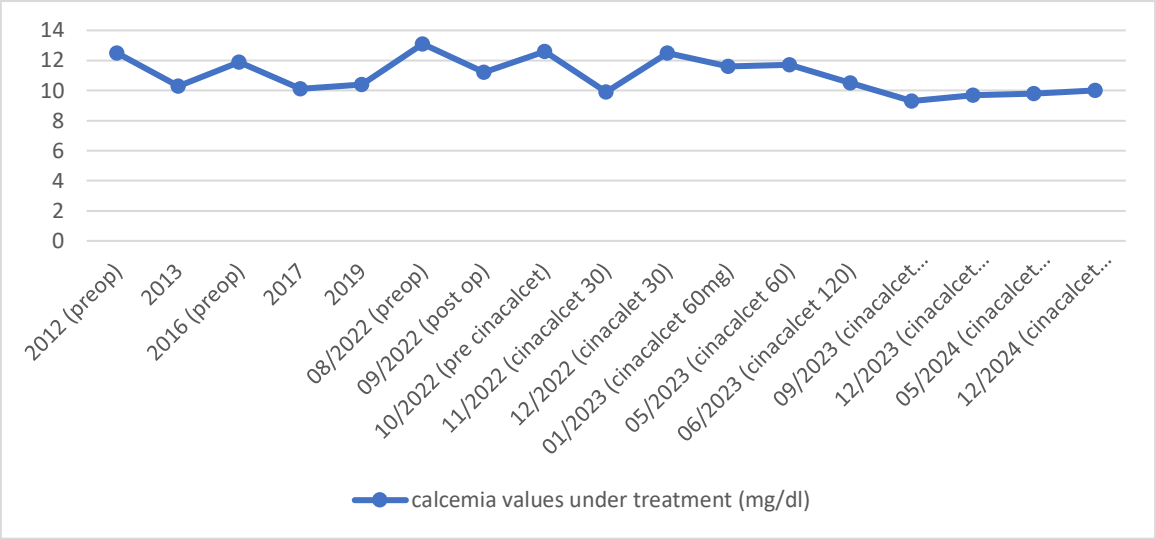


Figure 2 : 18F-Choline PET-CT images of the patient showing tracer uptakes in the parathyromatosis foci

Management of parathyromatosis and Outcome:

After detailed explanation of the treatment options, the patient declined further surgery and opted for medical therapy. She was started on cinacalcet (a calcimimetic) at 30 mg/day, which was progressively increased until achieving good biochemical control at a dose of 120 mg/day (see Graphic 1).



Graphic 1: Changes in serum calcium levels under treatment (mg/dl)

DISCUSSION

Parathyromatosis is defined as the presence of multiple aggregates of hyperplastic and hyperfunctional parathyroid tissue disseminated in the neck or upper mediastinum [7]. It represents one of the rarest causes of persistent or recurrent hyperparathyroidism [3]. Although relatively uncommon; awareness of parathyromatosis has increased over the past decades, as reflected in recent literature. A recent literature review identified 63 reported cases of parathyromatosis, either as isolated cases or as part of case series [8] ; the first one reported in 1975 by Palmer et al. [7].

The most commonly reported sites of parathyromatosis foci include the thyroid bed, parathyroid autotransplantation sites such as the forearm or the sternocleidomastoid muscle [4], and more rarely, the cervical subcutaneous fat, adjacent to the recurrent laryngeal nerve, paratracheal space, retrosternal region, carotid sheath, intertracheoesophageal space, intrathymic area, upper mediastinum, or thymus [3,5].

In line with these observations, our case demonstrated parathyromatosis foci located in the thyroid bed, the sternocleidomastoid muscle, and the paraesophageal region, consistent with previously reported locations.

Parathyromatosis is generally more frequent in women in their fifties, as was the case for our patient, and in individuals with end-stage renal disease or vitamin D deficiency [9]. Its time of onset in the literature varies widely, ranging from 5 months to 19 years [10].

Understanding the underlying mechanisms is crucial for accurate diagnosis and management. Two main pathophysiological mechanisms have been described. The secondary form, which is the most common and accounts for more than 92% of cases [9], is caused by intraoperative seeding of parathyroid adenoma or hyperplastic tissue, secondary to capsular rupture during surgery. The primary form is much rarer and is characterized by the presence of benign hyperplastic embryologic parathyroid remnants, often associated with genetic mutations and typically located in the thymus.

The hyperplasia of these parathyroid tissues may either be primary, as part of a syndromic context such as Multiple Endocrine Neoplasia type 1 (MEN1) [7], or secondary, due to hypocalcemia and vitamin D deficiency, conditions commonly observed in chronic kidney disease (CKD). This could explain the high prevalence of parathyromatosis in this patient population [9].

Moreover, alternative hypotheses have been proposed to explain the disease's behavior. The development of a low-grade malignancy has also been proposed as a potential mechanism, based on the presence of locally invasive behavior without distant metastases or overt histological signs of malignancy [5, 9].

As with all causes of persistent hyperparathyroidism, the diagnosis of parathyromatosis necessitates high-performance, multimodal imaging to confirm the presence of extensive tissue seeding and to guide potential reoperation [11]. Parathyromatosis poses significant diagnostic challenges due to its multifocality, small size, and atypical locations, which frequently cause conventional imaging to miss microscopic or deeply situated nodules [3]. This was exemplified in our patient, where several parathyromatosis foci remained undetected on conventional imaging due to their diminutive size. In this setting, 18F-Fluorocholine PET/CT, particularly when combined with 4D-CT, currently represents the most reliable modality for detecting lesions in complex or recurrent cases. Table 1 provides a summary and comparison of the diagnostic performance, advantages, and limitations of the principal imaging techniques employed in parathyromatosis detection.

Table 1: Diagnostic Modalities for Parathyromatosis – Comparative Overview (3) , (11-14)

Imaging Modality	Advantages	Drawbacks
Ultrasound (US)	-Sensitivity not clearly defined -Widely available, non-invasive, low cost -Effective for superficial nodules	-Low sensitivity for small or deeply located nodules -Operator-dependent -May not distinguish parathyroid from lymph nodes
Dual-phase 99mTc-sestamibi scintigraphy	-Standard tool for localizing solitary parathyroid adenomas -Familiar technique in most nuclear medicine centers	-Very limited yield in parathyromatosis due to small size and hyperplastic nature of lesions -Early washout leads to high false-negative rates
Subtraction imaging (123I/99mTc-Sestamibi)	-Improved specificity (59% vs 19%) through subtraction of thyroid uptake -Better diagnostic accuracy compared to dual-phase imaging	-Limited availability -Requires precise synchronization of radiotracers
SPECT/CT with wide-field acquisition and pinhole collimators	-Lower sensitivity than 123I/99mTc-Sestamibi -Enhances 3D anatomical localization -Facilitates detection of ectopic parathyroid tissue	-Radiation exposure -Reduced sensitivity for subcentimetric foci -Requires advanced nuclear imaging equipment
18F-Fluorocholine PET/CT	-High sensitivity and positive predictive value in persistent or recurrent PHPT with negative conventional imaging (96%) -Excellent spatial resolution	-Expensive -Limited accessibility -False positives may occur (e.g., lymph nodes, inflammatory tissue)

	-Accurate detection of multiple or ectopic foci	
18F-Fluorocholine PET/CT combined with 4D-CT	-Reduces false positives through combined anatomical and functional imaging -4D-CT enhances vascular phase detection and nodule characterization	-Combined radiation and contrast exposure -Less suitable in patients with renal impairment

Parathyroid carcinoma constitutes the primary differential diagnosis of parathyromatosis and must always be excluded in cases of multiple recurrences before confirming the latter. Biochemically, parathyroid carcinoma typically results in more severe hypercalcemia and markedly elevated parathyroid hormone (PTH) levels—commonly referred to as the "rule of threes."

A definitive diagnosis relies on histopathological examination of the surgical specimen. Macroscopically, parathyromatosis appears as multiple small nodules, ranging from a few millimeters up to less than 2 cm in size, with a pale yellowish or grayish color, and located in atypical regions. In contrast, parathyroid carcinoma typically presents as a solitary, large, whitish mass exceeding 3 cm, often with evidence of local tissue invasion. The presence of adherent fibrosis is not a reliable discriminative feature, as it may occur in both conditions, thereby complicating the diagnostic process [15].

Microscopically, the absence of encapsulation is a key distinguishing feature that helps differentiate parathyromatosis from both parathyroid adenoma and carcinoma [5, 15]. Parathyromatosis also lacks histological features of malignancy, such as capsular penetration, vascular invasion, and lymphatic spread. A mitotic index >5 per 10 high-power fields (HPF), cellular atypia, trabecular architecture, intratumoral necrosis, and fibrosis may be more suggestive of carcinoma, but none of these findings are independently definitive. In ambiguous cases, immunohistochemical analysis is required to establish a definitive diagnosis of parathyroid carcinoma, typically by demonstrating overexpression of retinoblastoma (Rb) protein and Galectin-3, along with loss of parafibromin expression [16].

Parathyromatosis is characterized by a slow-growing, benign clinical course, generally confined to the cervico-mediastinal region. Nevertheless, it can carry serious consequences due to complications arising from uncontrolled hyperparathyroidism, with mortality rates reported to be as high as 40% [17], thereby necessitating appropriate and timely therapeutic management.

As with other causes of persistent or recurrent hyperparathyroidism (HPT), the treatment of parathyromatosis is primarily surgical. The indication for surgery should be discussed in a multidisciplinary team meeting, carefully weighing the potential benefits against the higher risks inherent to reoperations [11]. Ideally, the procedure should be performed by an experienced endocrine surgeon in a specialized center equipped with recurrent laryngeal nerve neuromonitoring, intraoperative PTH assay, and, if possible, intraoperative fluorescence imaging [11].

Parathyromatosis requires an aggressive surgical approach, including bilateral cervical and mediastinal exploration via cervicotomy or sternotomy, with en-bloc resection of all visible foci. In secondary forms related to capsular rupture, extended procedures such as isthmolobectomy, lymph node dissection, and resection of subcutaneous tissue are recommended [11,15]. Surgical outcomes remain moderate, primarily due to the difficulty of identifying all foci intraoperatively, especially those not seen on

imaging or adherent to surrounding tissues(9). Multiple interventions are often needed, as shown in our case.

When surgery fails or is contraindicated, medical therapy becomes essential to control hyperparathyroidism and its complications [11]. Treatment choices depend on the goal, whether to lower calcium, suppress PTH, or manage organ damage.In mild, asymptomatic cases, conservative management with monitoring may be appropriate [11].

Among the most frequently and successfully used medications reported in the literature are calcimimetics [6, 9, 18, 19]. These are allosteric activators of the calcium-sensing receptor (CaSR) that reduce serum calcium levels by lowering PTH secretion and decreasing renal tubular calcium reabsorption without significantly increasing 24-hour calciuria or the risk of renal insufficiency [11]. They also exhibit anti-tumor properties by directly inhibiting parathyroid cell proliferation and promoting apoptosis [19]. However, several studies suggest that calcimimetics alone does not improve bone mineral density, and may not fully normalize bone turnover markers during prolonged therapy [20, 21].

Several other medical therapies have also been used for managing hypercalcemia and bone complications in parathyromatosis. These include bisphosphonates [18], active vitamin D analogs in patients with end-stage renal disease (with caution due to hypercalcemia risk) [19], and denosumab, a RANKL inhibitor, particularly effective in refractory cases when combined with cinacalcet [6].

Despite encouraging results reported in the literature, medical treatment of parathyromatosis still carries high failure rates [5]. In our patient's case, after the failure of two surgical attempts and refusal of a third procedure, treatment with cinacalcet was initiated, resulting in satisfactory disease control after dose adjustment.

Long-term monitoring remains essential, based on calcium and PTH levels, and assessment of end-organ impact. A new surgical intervention may be considered depending on the evolution of the biochemical profile, the occurrence of complications, or the findings of a new imaging work-up [11].

This case contributes insights to the literature by demonstrating the need for close monitoring and long-term follow-up of multi-operated patients for early recurrence detection, and the diagnostic utility of 18F-Fluorocholine PET/CT for identifying occult parathyromatosis foci. It also reinforces the importance of avoiding capsular rupture during surgery to prevent the occurrence of parathyromatosis and the potential effectiveness of cinacalcet in long-term management when surgery fails or is contraindicated.

CONCLUSION:

Parathyromatosis is an exceptional yet distinctive cause of recurrent or persistent hyperparathyroidism, primarily resulting from cervical seeding of parathyroid tissue following intraoperative fragmentation of a parathyroid adenoma. Its diagnosis remains challenging and requires a comprehensive localization work-up. Parathyroid carcinoma constitutes the main differential diagnosis and must be systematically excluded in suspected cases.

Management of parathyromatosis is complex and delicate, relying primarily on extensive surgical resection of all detectable foci. Clinicians should always consider parathyromatosis as a preventable surgical complication. Meticulous handling of parathyroid adenomas is essential to avoid capsular rupture and cellular seeding, which may lead to irreversible disease recurrence and the need for complex reoperations.

Medical therapy serves as an adjunct or alternative in cases of surgical failure or contraindications, though its efficacy varies widely. Given the high recurrence rates after treatment, regular long-term monitoring is essential.

This case provides a rare illustration of long-term disease evolution and highlights the potential effectiveness of cinacalcet as a non-surgical therapeutic alternative, offering durable biochemical when surgery is no longer feasible.

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