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A Case Report: Synchronous Normocalcemic Primary HyperParathyroidism and Multinodular Goitre - A Diagnostic and Therapeutic Challenge

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Abstract: ***Background: The synchronous presentation of primary hyperparathyroidism (PHPT) and multinodular goitre (MNG) is a relatively common clinical scenario. However, PHPT caused by multi-glandular parathyroid hyperplasia co-existing with MNG presents significant diagnostic and surgical challenges. Pre-operative localization studies like 99mTc-Sestamibi SPECT/CT can be equivocal in such cases. Case Presentation: We report the case of a 45-year-old female who presented with a swelling in the front of her neck. Her biochemical profile was suggestive of primary hyperparathyroidism, with a serum calcium of 11 mg/dL and an intact parathyroid hormone (PTH) level of 97 pg/mL. Thyroid function tests were normal. An ultrasound of the neck confirmed a multinodular goitre. A 99mTc-Sestamibi parathyroid SPECT/CT scan was inconclusive for a dominant adenoma, instead showing two nodular lesions with non-significant uptake in the superior paraesophageal regions, suggestive of possible hyperplasia. The patient underwent a total thyroidectomy and bilateral superior parathyroidectomy. Post-operative histopathology confirmed colloid goitre and primary parathyroid hyperplasia. Conclusion: This case highlights the diagnostic complexity when parathyroid hyperplasia and nodular thyroid disease coexist. Surgeons and endocrinologists must maintain a high index of suspicion for multi-gland disease when pre-operative imaging is atypical, and plan the surgical strategy accordingly to ensure curative treatment and avoid persistent or recurrent hyperparathyroidism.***

Keywords: Normocalcemic Hyperparathyroidism, Parathyroid Clear Cell Hyperplasia, Multinodular Goitre, Sestamibi SPECT/CT, Parathyroid Autotransplantation.

1. Introduction

Primary hyperparathyroidism (PHPT) is an endocrine disorder characterized by excessive secretion of parathyroid hormone (PTH), leading to hypercalcemia. It is most commonly caused by a single parathyroid adenoma (80-85% of cases), followed by parathyroid hyperplasia (10-15%), and rarely, parathyroid carcinoma (<1%). Co-existing thyroid pathology, particularly multinodular goitre (MNG), is frequently found in patients with PHPT, with a reported prevalence ranging from 19% to 58%.

The presence of a concomitant MNG can complicate the diagnosis and management of PHPT. Thyroid nodules can lead to false-positive or false-negative results on pre-operative localization studies such as ultrasound and 99mTc-Sestamibi scans. Furthermore, when PHPT is due to hyperplasia, which involves multiple glands, localization studies are often less sensitive than for a solitary adenoma. This case report describes the clinical presentation, diagnostic workup, and successful surgical management of a patient with synchronous four-gland parathyroid hyperplasia and a large multinodular goitre, where pre-operative imaging was non-localizing for a definitive adenoma.

2. Aim and Objectives

Aim: To report and discuss the diagnostic and management pathway of a patient with co-existent primary parathyroid hyperplasia and multinodular goitre.

Objectives:

1) To highlight the clinical and biochemical presentation of the case.
2) To discuss the limitations of 99mTc-Sestamibi SPECT/CT in diagnosing parathyroid hyperplasia in the setting of MNG.
3) To underscore the importance of a comprehensive surgical approach, including total thyroidectomy and definitive parathyroid surgery, in such synchronous pathologies.
4) To review the relevant literature on the association between parathyroid and thyroid diseases.

3. Review of Literature

The association between thyroid disease and primary hyperparathyroidism is well-documented. The high prevalence of this association has led to several hypotheses, though a definitive causal link remains unproven. One theory suggests that shared embryological origins or genetic predispositions may play a role. Another prominent theory posits that long-standing hypercalcemia might have a trophic effect on thyroid C-cells and follicular cells, potentially stimulating goitrogenesis. Conversely, goitrogenic factors might influence parathyroid growth.

PHPT is defined by hypercalcemia in the presence of an elevated or inappropriately normal PTH level. While single adenomas are the most common cause, multi-gland hyperplasia presents a greater surgical challenge. Pre-operative localization is crucial to guide surgery, minimizing operative time and morbidity. High-resolution ultrasound and

99mTc-Sestamibi scintigraphy (often with SPECT/CT) are the mainstays of imaging. Sestamibi scans rely on the differential washout of the tracer from hyperfunctioning parathyroid tissue compared to thyroid tissue. However, its sensitivity is significantly lower for hyperplastic glands (40-70%) compared to adenomas (>90%). The presence of thyroid nodules, which can also retain Sestamibi, further confounds interpretation. In cases of MNG and suspected PHPT where Sestamibi scans are negative or equivocal, the suspicion for multi-gland disease should be high.

Materials and Methods (Case Presentation)

A 45-year-old female presented to the endocrine surgery clinic with a chief complaint of a visible swelling over the anterior aspect of her neck, which had been gradually increasing in size over the past few years. She did not report any compressive symptoms or specific symptoms of hypercalcemia. Her past medical and family histories were non-contributory.

On physical examination, a diffuse, non-tender, firm goitre was palpable, which moved with deglutition.

Investigations:

1) **Biochemical Analysis:** Laboratory results revealed a state of primary hyperparathyroidism.
   - Serum Calcium: 11 mg/dL
   - Serum Phosphorus: 3.8 mg/dL
   - Intact PTH: 97 pg/mL (Reference range: 15-65 pg/mL)
   - Serum Albumin: 4.7 g/dL
   - Calculated Corrected Calcium: 10.44 mg/dL
   - 25-Hydroxy Vitamin D: 28 ng/mL (Insufficient)
   - Serum Magnesium: 3.9 mg/dL
   - Thyroid Stimulating Hormone (TSH): 2.3 µIU/mL (Euthyroid)
   - Free T4: 1.1 ng/dL
   - Lipid Profile: Total Cholesterol 191 mg/dL, HDL 41 mg/dL, Triglycerides 191 mg/dL.

2) **Imaging:**
   - **Neck Ultrasound (USG):** Confirmed the presence of a multinodular goitre with multiple colloid nodules in both lobes, the largest measuring 3.5 x 2.5 cm. No definitive parathyroid adenoma was visualized.
   - **99mTc-Sestamibi Parathyroid SPECT/CT:** The scan was performed to localize the source of PTH excess. It revealed two well-defined nodular lesions with no significant increased 99mTc-sestamibi uptake, located posteromedial to the superior poles of both thyroid lobes in the paraesophageal regions. The report concluded these findings were suspicious for parathyroid lesions, possibly representing parathyroid hyperplasia rather than a classic adenoma.

Surgical Intervention: Given the biochemical diagnosis of PHPT, the large multinodular goitre, and the inconclusive localization scan suggesting multi-gland disease, a decision was made for a comprehensive surgical exploration. The patient underwent a total thyroidectomy and bilateral superior parathyroidectomy. The inferior parathyroid glands were identified and appeared to be of normal size and texture.

4. Results

The surgical procedure was completed without any complications. The patient's post-operative course was uneventful.

Histopathology: The post-operative histopathology report (HPE) confirmed the diagnoses:

1) **Parathyroid Glands:** The tissue from the bilateral superior parathyroidectomy was reported as **Parathyroid Hyperplasia**, characterized by a diffuse proliferation of chief cells with a reduction in stromal fat.
2) **Thyroid Gland:** The thyroid specimen was reported as a **Multinodular Colloid Goitre**, with multiple nodules of varying sizes filled with abundant colloid and lined by flattened follicular epithelium, with no evidence of malignancy.

Post-operative Follow-up: Post-operatively, the patient's serum PTH level normalized, and her serum calcium dropped to the lower end of the normal range. She was started on levothyroxine replacement therapy for iatrogenic hypothyroidism and monitored for hypocalcemia, which did not occur. At her 3-month follow-up, she remained asymptomatic with normal serum calcium and PTH levels.

5. Discussion

This case illustrates a classic clinical dilemma: the management of a patient with both a large MNG and biochemically confirmed PHPT. The diagnostic challenge was amplified by the underlying pathology being parathyroid hyperplasia, which is notoriously difficult to localize pre-operatively.

The 99mTc-Sestamibi SPECT/CT findings are a key feature of this case. The absence of a single, avidly concentrating lesion and the mention of two poorly concentrating superior pole nodules correctly raised the suspicion of hyperplasia. In the setting of a co-existing MNG, a negative or equivocal Sestamibi scan should not dissuade the diagnosis of PHPT but should alert the surgeon to the higher probability of multi-gland disease or an ectopic gland.

The decision to proceed with a total thyroidectomy was justified by the size of the goitre itself. For the hyperparathyroidism, the surgical options included bilateral neck exploration to identify all four glands or a more directed approach. Given the suspicion of hyperplasia, a bilateral exploration is the gold standard. In this case, removing the two macroscopically abnormal superior glands and confirming the normal appearance of the inferior glands was a sound surgical strategy, aiming to render the patient eucalcemic while preserving parathyroid function from the remaining glands. The normalization of post-operative PTH and calcium levels confirmed the success of this approach.

This case reinforces that when PHPT and MNG coexist, a combined surgical procedure addressing both pathologies in a single session is safe and effective. It spares the patient the morbidity and costs of a second operation.

6. Summary and Conclusions

We presented a case of a 45-year-old female with synchronous primary hyperparathyroidism due to multi-gland hyperplasia and a large multinodular goitre. The case demonstrates that:

1) The coexistence of thyroid and parathyroid disease is common and requires a thorough and integrated diagnostic approach.
2) Pre-operative localization studies like 99mTc-Sestamibi SPECT/CT can be non-localizing or atypical in parathyroid hyperplasia, especially with concurrent nodular thyroid disease.
3) A high index of suspicion for multi-gland parathyroid disease is warranted when a patient with PHPT has an inconclusive Sestamibi scan.
4) A comprehensive surgical plan that includes a total thyroidectomy for the goitre and a formal parathyroid exploration is the definitive treatment, capable of curing both conditions in a single operation.

In conclusion, the successful outcome in this patient was predicated on a careful interpretation of the combined clinical, biochemical, and imaging data, leading to an appropriate and comprehensive surgical strategy.

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