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Coexistence of Primary Hyperparathyroidism and Familial Hypocalciuric Hypercalcemia: A Case Analysis and Diagnostic Review

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Abstract **Case Report**

The concurrent manifestation of Primary Hyperparathyroidism (PHPT) and Familial Hypocalciuric Hypercalcemia (FHH) within a single individual represents a diagnostic paradox. FHH is typically an autosomal dominant, benign operational shift in the homeostatic set-point of calcium, driven by inactivating germline mutations of the calcium-sensing receptor (CaSR) gene, requiring conservative management. Conversely, PHPT is a common acquired disorder of autonomous parathyroid hormone (PTH) hypersecretion requiring targeted surgical exploration to avoid renal and skeletal decompensation. This comprehensive article reviews the specific clinical case of a 56-year-old female patient presenting with severe hypercalcemia (110.5 mg/L) and elevated PTH (240 pg/mL) accompanied by persistent, verified hypocalciuria (75 mg/24h) and a localized 12x9 mm lower left parathyroid adenoma. We dissect the deep molecular cross-talk, tracking how chronic baseline parathyroid tissue stimulation in FHH may facilitate somatic clonal expansion, leading to superimposed PHPT adenomas. Furthermore, we analyse why traditional screening parameters like the fractional excretion of calcium fail during dual-pathology overlap, concluding with clinical guidelines to prevent redundant, harmful cervical explorations.

Key words: Familial Hypocalciuric Hypercalcemia, Primary Hyperparathyroidism.

INTRODUCTION

Primary Hyperparathyroidism (PHPT) represents the third most common endocrine disorder globally, presenting as an acquired autonomous tissue dysfunction, predominantly localized to a solitary benign adenoma or diffuse glandular hyperplasia. Biochemically, PHPT triggers elevated or inappropriately normal parathyroid hormone (PTH) levels, downstream hypercalcemia, and classic hypercalciuria resulting from overwhelmed renal tubular reabsorption capacity.[1]

In contrast, Familial Hypocalciuric Hypercalcemia (FHH) is a rare, non-progressive genetic disorder inherited in an autosomal dominant fashion, characterized by mild-to-moderate asymptomatic hypercalcemia, paradoxically low urinary calcium excretion, and normal or slightly elevated serum PTH. [2] Operating on classic medical principles, these two etiologies are traditionally treated as strict mutual differentials. However, cutting-edge molecular surveillance reveals that these conditions can physically overlap. The development of structural primary hyperparathyroidism (PHPT) via secondary clonal mutations in a patient with underlying germline familial hypocalciuric hypercalcemia (FHH) alters classic biochemical profiles, complicating the diagnostic evaluation for endocrinologists and endocrine surgeons.

PATIENT ET OBSERVATION

A 56-year-old female patient was evaluated at the Department of Endocrinology, CHU Mohamed VI, Marrakech, Morocco, presenting with pronounced hypercalcemia associated with biochemistry strongly suggestive of hyperparathyroidism. Overt secondary clinical phenotypes such as nephrolithiasis, severe bone pain, or cognitive deficits were not actively driving the presentation. Advanced biochemical profiling established the following specific values:

- Corrected Serum Calcium: 110.5 mg/L (Reference Value [RV]: 86–100 mg/L), confirming distinct, sustained hypercalcemia.
- Intact PTH (1-84): 240 pg/mL (RV: 9.20–44.6 pg/mL), demonstrating severe, autonomous parathyroid overactivity.
- 24-Hour Urinary Calcium Excretion: 75 mg/24h (RV: 100–320 mg/24h), indicating profound, unexpected hypocalciuria.

To achieve structural localization, a cervical parathyroid scintigraphy was executed, successfully localizing a clear 12x9 mm hyperfunctioning parathyroid adenoma on the lower left parathyroid gland.

The coexistence of explicit structural pathology with severe PTH hypersecretion normally mandates an absolute referral for targeted parathyroidectomy. However, the patient's biochemical evaluation presented an alarming paradox: severe hypercalcemia coupled with high circulating PTH should physiologically result in massive hypercalciuria due to the saturation of renal calcium reabsorptive channels. The patient's 24-hour urinary calcium excretion of 75 mg/24h was entirely conflicting. Recognizing this discrepancy, the clinical team deferred immediate surgery and instituted strict longitudinal monitoring of blood calcium levels, urinary profiles, and skeletal parameters. The profound hypocalciuria was rigorously verified and confirmed across two separate, sequential 24-hour urine collections. Despite the presence of a functional parathyroid adenoma, the patient maintained a biochemical profile consistent with hypocalciuria, strongly suggesting a diagnosis of Marx syndrome.

DISCUSSION

The co-development of an autonomous parathyroid adenoma within an individual harboring a germline FHH variant is a precise, mechanistically driven sequence. FHH Type 1 is caused by heterozygous inactivating mutations in the CaSR gene located on chromosome 3q21.1. The CaSR is a G-protein-coupled receptor heavily localized to the plasma membranes of parathyroid chief cells and renal tubular epithelial cells. In its normal configuration, extracellular calcium binding stimulates Gq/11 and Gi pathways, reducing intracellular cAMP and directly inhibiting PTH vesicle exocytosis.[3]

When a germline mutation rendering the CaSR partially non-functional is present, the receptor's structural sensitivity is blunted. The parathyroid chief cells require a significantly elevated extracellular calcium concentration to initiate the intracellular cascade required to suppress PTH secretion. Consequently, the parathyroid glands experience a permanent, lifelong perception of baseline 'hypocalcemia'. This unremitting trophic stimulation induces continuous cellular proliferation, culminating in diffuse chief cell hyperplasia. [4]

Across decades of life, this hyperplastic tissue represents an expanding cellular mass under high replication stress. If a single hyperplastic cell sustains a somatic 'second hit'—such as a clonal mutation or loss of heterozygosity in cell cycle regulators, MEN1 tumor suppressors, or oncogenic pathways—it gains a distinct proliferative advantage. [4] This event initiates localized, autonomous clonal expansion, culminating in a distinct parathyroid adenoma or lipoadenoma. At this clinical junction, the patient expresses a mixed phenotype: the autonomous tumor drives serum calcium and PTH levels significantly above the patient's baseline FHH equilibrium, while the remaining non-adenomatous parathyroid tissue and renal tubules retain the underlying, desensitized FHH architecture.

The primary obstacle to identifying this combined pathology is the failure of the Calcium-to-Creatinine Clearance Ratio (CCCR), also termed the Fractional Excretion of Calcium (FeCa).

In pure FHH, because the CaSR in the thick ascending limb of the loop of Henle is desensitized, the kidney exhibits an extraordinarily high rate of tubular calcium reabsorption despite elevated serum levels, typically yielding a FeCa well below 0.01.

In isolated PHPT, the massive filtered calcium load overpowers renal tubular reabsorption, causing marked hypercalciuria and a FeCa typically above 0.02. [5] When PHPT superimposes on FHH, the hyperfunctioning adenoma drives serum calcium to extreme heights. This massive filtered load can overwhelm the desensitized FHH-mutated receptors, elevate urinary calcium excretion and pushing the calculated FeCa into the misleading 'gray zone' (0.01–0.02) or even into the hypercalciuric range (>0.02). [6] This completely masks the underlying germline FHH mutation. In our case, the patient's severe hypercalcemia failed to overwhelm renal retention, maintaining a profoundly low 24-hour urinary output of 75 mg, which served as the primary clinical indicator of the underlying dual disease state.

The identification of this dual pathology mandates a complete restructuring of traditional therapeutic goals. In classic standalone PHPT, surgical parathyroidectomy aims for full restoration of normocalcemia. However, in a patient with a concurrent germline FHH variant, management is typically limited to observation and patient reassurance, as surgical intervention is contraindicated and ineffective in addressing the condition.

Parathyroidectomy targeted exclusively to the structurally localized autonomous adenoma is indicated to protect structural systems from aggressive fluctuating

spikes without introducing complete structural failure. Pharmacological management via allosteric modulators like Cinacalcet-HCl can safely augment receptor response when surgery remains inappropriate.[7]

CONCLUSION

The coexistence of primary hyperparathyroidism (PHPT) and familial hypocalciuric hypercalcemia (FHH) represents a rare clinical complex that necessitates a critical reassessment of standard diagnostic paradigms. The hallmark of this dual pathology is the persistent observation of hypocalciuria despite concomitant hyperparathyroidism and the structural confirmation of an autonomous adenoma. Consequently, integrating early genetic screening for *CaSR* variants into the diagnostic evaluation of these complex cases is essential for ensuring accurate clinical management and preventing unnecessary or ineffective surgical interventions.

Conflicts of Interest: The authors declare no conflicts of interest.

Author Contributions

All authors have contributed to the conduct of this work. All authors also declare that they have read and approved the final version of the manuscript.

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