

# Severe Hypercalcemia due to Primary Hyperparathyroidism with MEN 2A

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## ABSTRACT

**Introduction:** Severe hypercalcemia due to primary hyperparathyroidism (PHPT) is rare in the setting of MEN 2A.

**Materials and methods:** Two patients with MEN 2A and severe hypercalcemia were identified recently. Their clinical presentation, evaluation, surgical management and outcomes are reviewed.

**Results:** Two patients with MEN 2A were identified with severe hypercalcemia secondary to a parathyroid adenoma. Calcium levels were elevated to 12.7 mg/dL and 15.1 mg/dL, respectively (normal range = 8.9-10.1 mg/dL). In each case, a single parathyroid adenoma was identified and surgically excised with normalization of parathyroid and calcium levels postoperatively. Clinical manifestations at the time of diagnosis included constipation, polyuria, hypercalciuria, and decreased bone mineral density.

**Conclusion:** Severe elevation of serum calcium is a rare presentation of PHPT in MEN2A. The differential diagnosis should include parathyroid adenoma, hyperplasia and parathyroid carcinoma. Early surgical management is essential in the treatment of hyperparathyroidism with severe hypercalcemia to prevent further complications.

**Keywords:** MEN 2A, Hyperparathyroidism, Hypercalcemia.

## INTRODUCTION

Multiple endocrine neoplasia 2A (MEN 2A) is associated with medullary thyroid cancer, pheochromocytomas, and parathyroid adenomas. Germline gain of function mutations of the RET protooncogene, located on chromosome 10q11.2, are responsible for these clinical abnormalities. Primary hyperparathyroidism (PHPT) occurs in 20 to 30% of patients with MEN 2A most often after the 3rd decade of life.<sup>1,2</sup> Parathyroid hormone and serum calcium elevation are generally mild.<sup>3,4</sup> Current diagnostic and therapeutic treatment strategies involve a focused surgical approach with resection of only grossly abnormal glands. Preoperative work up includes ultrasound of the neck and sestamibi scan, which allows for a targeted surgical management. Early surgical therapy can prevent sequelae of severe hypercalcemia.<sup>5,6</sup>

## MATERIALS AND METHODS

Two patients with MEN 2A and severe hypercalcemia were recently identified. Their clinical presentation, evaluation, surgical management and outcomes are reviewed.

## RESULTS

Two patients with MEN 2A mutations presented with severe hypercalcemia. The first patient is a 17-year-old adolescent with a RET proto-oncogene mutation in codon 634 (TGC to CGC). He had previously undergone a prophylactic thyroidectomy at age 5 with histology revealing C-cell hyperplasia. Routine serum calcium measurements aged between 8-12 years ranged from 8.9 to 10.4 mg/dL (age adjusted reference range 9.5-10.4 mg/dL).

In November 2008 (age 16 years), his calcium was found to be elevated at 11.8 mg/dL with a PTH of 77 pg/mL (reference range 15-65 pg/mL). Repeat calcium in 2009 (age 17 years) was elevated to 12.7 mg/dL with a PTH of 101 pg/mL. The manifestations of PHPT included fatigue, hypercalciuria (calcium to creatinine ratio on random urine specimen 0.4, normal < 0.2), and a below average bone density in his lumbar spine with a Z-score of -1.9 (L1-L4 vertebrae). Preoperative ultrasound revealed a 2.1 × 1.0 × 0.7 cm hypoechoic solid nodule in the right tracheoesophageal groove. Sestamibi results were equivocal for a parathyroid adenoma. A fine needle aspiration was performed of this mass and cytology was consistent with a parathyroid adenoma. A PTH level was obtained of the FNA

effluent with a level of 664 pg/mL. Cervical exploration via a right lateral approach was performed with intraoperative PTH monitoring. PTH levels decreased from 125 pg/mL at baseline to 29 pg/mL at 10 minutes postoperatively. Pathology revealed a parathyroid adenoma measuring  $2.0 \times 1.8 \times 0.8$  cm and weighing 1130 mg.

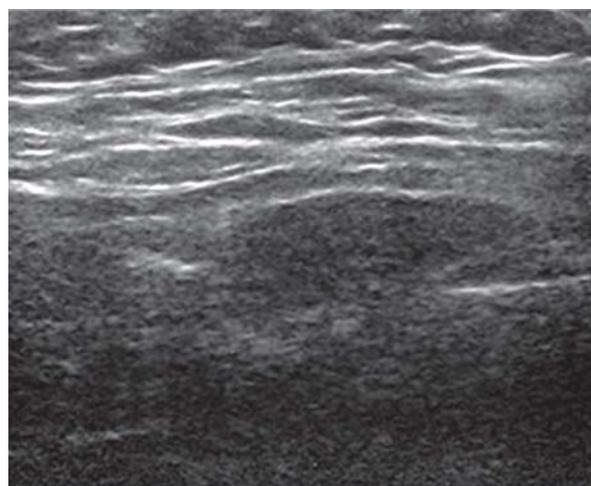
The second patient is a 32-year-old woman with MEN 2A due to a mutation in codon 618 of the RET proto-oncogene resulting in a cysteine to serine alteration. A thyroidectomy was performed in 1999 (age 21 years) with the finding of a localized medullary thyroid microcarcinoma. Her left inferior parathyroid gland was removed inadvertently at the time of operation due to its subcapsular location within the thyroid. 10 years later, she presented with elevated calcium level of 14.4 mg/dL and a parathyroid hormone level of 357 pg/mL. Symptoms at this time included fatigue, depressed mood, constipation and polyuria. Her calcium continued to rise to a peak of 15.1 mg/dL, and she was treated in the emergency room with intravenous fluids to lower her calcium levels. In addition, she was treated with cinacalcet before surgery with modest reduction in her calcium level to 14.0 mg/dL. Ultrasound of her neck showed a large parathyroid tumor in the left tracheoesophageal groove (Fig. 1). A sestamibi scan revealed a focus of increased uptake on the left side of the neck. Due to the severity of her hypercalcemia, a preoperative diagnosis of parathyroid carcinoma was considered. A cervical exploration via a left lateral approach was performed with intraoperative PTH monitoring. Her baseline PTH was 428 pg/mL and dropped to 84 pg/mL at 10 minutes and 37 pg/mL at 90 minutes, post-resection. Cervical exploration confirmed a right superior well circumscribed parathyroid adenoma with hyperplastic cells (Figs 2A and B) measuring  $2.1 \text{ cm} \times 1.0 \text{ cm} \times 1.0 \text{ cm}$  and weighing 2030 mg (Fig. 3).

In both cases, 50 to 100 mg of parathyroid tissue was autotransplanted into a subcutaneous pocket of the anterior chest wall. Parathyroid hormone fell to undetectable levels within 24 hours after surgery and recovered to normal levels post-operatively. In the first case, calcium levels are within normal limits at 9.0 mg/dL three months after surgery. The second patient has a calcium level of 8.6 mg/dL 30 days after surgery. She required intravenous calcium in the immediate postoperative period due to hypocalcemia secondary to bone hunger syndrome after parathyroidectomy, but her levels have stabilized on oral calcium supplementation.

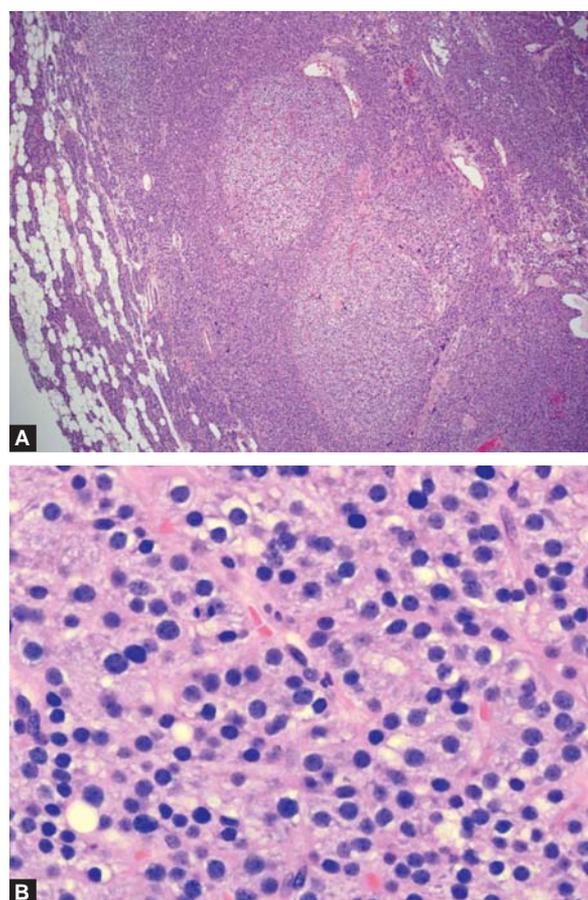
Of note, both patients were screened for the presence of pheochromocytoma before surgical management of their PHPT. Urine metanephrines and normetanephrines were within normal range for both patients.

## DISCUSSION

PHPT in MEN 2A is often asymptomatic or presents with mild hypercalcemia and elevated parathyroid hormone level. An extreme elevation of serum calcium is unusual. While it is usually noted that PHPT develops after the third decade,<sup>1,2</sup> both



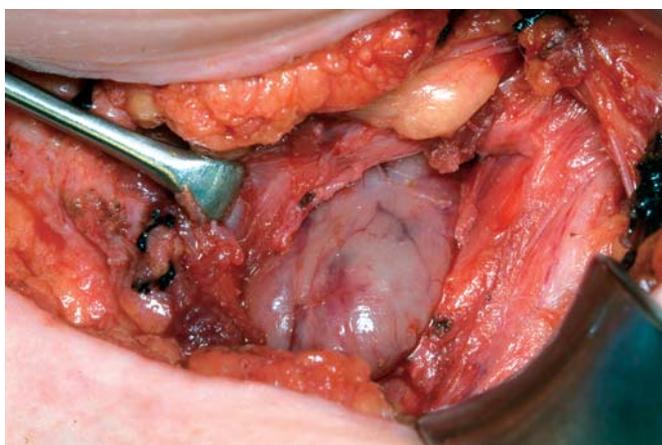
**Fig. 1:** Soft tissue ultrasound of the neck showing a hypoechoic nodule consistent with a parathyroid adenoma



**Figs 2A and B:** Parathyroid adenoma at (A) 40 and (B) 100x magnification showing a rim of normal parathyroid tissue around hyperplastic cells

of our patients developed biological and clinical signs of the disease in the 2nd and 3rd decade of life. The younger patient did have a mutation in codon 634, the codon most commonly associated with higher frequency of PHPT.

Multiple retrospective analyses have shown that PHPT in MEN2A mutations manifests as a mild form of the disease.<sup>3,4</sup> The French Association of Endocrine Surgeons and the French Calcitonin Tumors Study Group evaluated 56 patients affected by PHPT among 249 MEN 2A patients. PHPT was



**Fig. 3:** Intraoperative photo of a left parathyroid adenoma adjacent to the trachea in the remnant thyroid bed

asymptomatic in 68% of the patients. Serum calcium levels ranged from 8.8 to 14.8 mg/dL with a median of 11.3 mg/dL.<sup>7</sup>

Raue et al performed a retrospective multicentered case series of 60 patients with MEN2A and PHPT based on the registered cases from the EUROMEN study group from 1972 to 1993. Primary hyperparathyroidism was asymptomatic in 84% of the patients while 15% suffered from renal stones, serum calcium was slightly elevated in 69% of patients at a median level of 11.6 mg/dL  $\pm$  0.8 mg/dL and normal in 16% of subjects.<sup>8</sup>

A review of our own experience has shown that patients with MEN 2A have a lower preoperative serum calcium level and fewer symptoms and complications from hypercalcemia compared to patients with MEN 1. Median preoperative serum calcium was 10.7 mg/mL (10.2-13.5 mg/mL) in MEN 2A patients while the median value for MEN 1 was 11.3 mg/mL (9.9-14.1 mg/dL). All patients with MEN 2A achieved complete cure whether undergoing a total, subtotal or lesser resection, and with a mean follow-up of 5.8 years, there were no recurrences in the MEN 2A cohort.<sup>9</sup>

Currently, prospective screening of mutations allows for early detection of hypercalcemia. PHPT has evolved from one presenting with the classic triad "painful bones, kidney stones, and abdominal groans" to one where the symptoms are subtle and detection commonly occurs as a result of routine biochemical testing.<sup>10</sup> Periodic testing for high-risk individuals such as MEN 1 and MEN 2 kindreds may prevent severe disease with early detection and intervention.

Despite these developments, an acute rise in calcium is still possible in MEN 2A patients and should be treated appropriately with medical management and concomitant surgical evaluation for definitive treatment. The differential for acute hypercalcemia should include parathyroid carcinoma, which consistently displays both a higher calcium and parathyroid level than benign disease.<sup>11</sup> Although rare in both the general population and MEN 2A kindreds, a diagnosis of parathyroid carcinoma requires a more aggressive surgical approach.<sup>12,13</sup>

PHPT in MEN 2A results from single adenoma formation or multigland hyperplasia, however definitive treatment is removal of only grossly abnormal glands. In the reoperative

setting, autotransplantation of parathyroid tissue is an important consideration to reduce the risk of permanent hypoparathyroidism.<sup>14</sup>

In addition to evaluating patients for PHPT, it is important to screen for a concurrent pheochromocytoma. If urinary or plasma metanephrines and catecholamines are elevated, imaging, pharmacologic blockade and adrenalectomy should be performed before proceeding to parathyroidectomy.

## CONCLUSION

Severe hypercalcemia is an uncommon presentation of PHPT in MEN 2A. A focused surgical approach targeting abnormal parathyroid glands is effective in correcting PHPT and hypercalcemia. Once abnormal glands are resected, PHPT in MEN 2A is readily cured and recurrence is rare.

## REFERENCES

1. Wells SA, Donis-Keller H. Current perspectives on the diagnosis and management of patients with multiple endocrine neoplasia type 2 syndromes. *Endocrino Metab Clin North Am* 1994;23(1):215-28.
2. Mulligan LM, Kwok JBJ, Healy CS, et al. Germ-line mutations of the RET proto-oncogene in multiple endocrine neoplasia type 2a. *Nature* 1993;363(6428):458-60.
3. Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. *J Clin Endocrinol Metab* 2001;86(12):5658-71.
4. Carling T, Udelsman R. Parathyroid surgery in familial hyperparathyroid disorders. *J Intern Med* 2005;257(1):27-37.
5. Chan AK, Duh QY, Katz MH, et al. Clinical manifestations of primary hyperparathyroidism before and after parathyroidectomy: A case-control study. *Ann Surg* 1995;222(3):402-14.
6. Hedback G, Oden A, Tisell LE. The influence of surgery on the risk of death in patients with primary hyperparathyroidism. *World J Surg* 1991;15(3):399-407.
7. Kraimps JL, Denizot A, Carnaille B, et al. Primary hyperparathyroidism in multiple endocrine neoplasia type IIa: Retrospective French multicentric study. Groupe d'Etude des Tumeurs à Calcitonine (GETC, French Calcitonin Tumors Study Group), French Association of Endocrine Surgeons. *World J Surg* 1996;20(7):808-12.
8. Raue F, Kraimps JL, Dralle H, Cougard, et al. Primary hyperparathyroidism in multiple endocrine neoplasia type 2A. *J Intern Med* 1995;238(4):369-73.
9. O'Riordain DS, O'Brien T, Grant CS, Weaver A, Gharib H, van Heerden JA. Surgical management of primary hyperparathyroidism in multiple endocrine neoplasia types 1 and 2. *Surgery* 1993;114(6):1031-37.
10. Eigelberger MS, Cheah WK, Ituarte PH, Streja L, Duh QY, Clark OH. The NIH criteria for parathyroidectomy in asymptomatic primary hyperparathyroidism: Are they too limited? *Ann Surg* 2004;239(4):528-35.
11. Robert JH, Trombetti A, Garcia A, et al. Primary hyperparathyroidism: Can parathyroid carcinoma be anticipated on clinical and biochemical grounds? Report of nine cases and review of the literature. *Ann Surg Oncol* 2005;12(7):526-32.
12. Marocci C, Cetani F, Rubin MR, Silverberg SJ, Pinchera A, Bilezikian JP. Parathyroid carcinoma. *J Bone Miner Res* 2008;23(12):1869-80.
13. Levin KE, Galante M, Clark OH. Parathyroid carcinoma versus parathyroid adenoma in patients with profound hypercalcemia. *Surgery* 1987;101(6):649-60.
14. Bartsch DK, Rothmund M. Reoperative surgery for primary hyperparathyroidism. *Br J Surg* 2009;96(7):699-701.