Section: General Medicine

Case Series

RARE PRESENTATION OF HYPERPARATHYROIDISM: CASE SERIES

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ABSTRACT

Background: Primary hyperparathyroidism (PHPT) commonly presents with nephrolithiasis and hypercalcemia; however, several atypical manifestations remain underrecognized. We describe three uncommon clinical presentations of PHPT that highlight the diagnostic challenges and the need for a high index of suspicion.

Cases: The first case involved a 50-year-old man presenting with hypokalemic paralysis. Evaluation revealed severe hypokalemia, hypercalcemia, markedly elevated parathyroid hormone (PTH), normal anion gap metabolic acidosis, alkaline urine, and bilateral medullary nephrocalcinosis, consistent with distal renal tubular acidosis (dRTA) secondary to PHPT. Sestamibi scintigraphy localized a left inferior parathyroid adenoma. The second case was a 50-year-old woman with Graves' disease who presented with thyrotoxicosis, hypercalcemia, and elevated PTH. Imaging demonstrated a left inferior parathyroid adenoma. Following treatment of thyrotoxicosis with carbimazole, the elevated PTH became more apparent, illustrating the masking effect of hyperthyroidism on PHPT. The third case involved a 27-year-old man with MEN2A syndrome, previous pheochromocytoma, recurrent renal calculi, persistently elevated PTH despite normal serum calcium, and a positive RET Cys634Arg mutation. Histopathology after parathyroidectomy confirmed a left inferior parathyroid adenoma, representing normocalcemic PHPT.

Discussion: These cases demonstrate the diverse spectrum of PHPT beyond classical hypercalcemia. Hypercalciuria-induced nephrocalcinosis may result in distal RTA and hypokalemic paralysis. Coexisting Graves' disease can obscure biochemical features of PHPT and reduce sestamibi scan sensitivity until euthyroidism is achieved. In MEN2A, PHPT may present in a normocalcemic state, emphasizing the importance of serial biochemical assessment and exclusion of secondary causes of elevated PTH before diagnosis.

Conclusion: Clinicians should recognize these rare manifestations of PHPT to avoid delayed diagnosis and treatment. Early identification of atypical presentations, appropriate biochemical evaluation, targeted imaging, and timely surgical intervention can significantly improve patient outcomes and prevent long-term complications.

Keywords: Primary hyperparathyroidism.

INTRODUCTION

The most common clinical feature of primary hyperparathyroidism is nephrolithiasis, that is seen in 50% of cases. Hyperparathyroidism can affect proximal and distal renal tubular functions. Distal RTA is seen in cases of primary hyperparathyroidism. Significant hypercalciuria leads to renal tubular dysfunction is one of the proposed mechanisms for same.[1] Graves' disease and primary hyperparathyroidism are commonly reported in clinical practice. However, coexistence of these two conditions is reported rarely in the

literature. First case of concomitant hyperparathyroidism and Graves' disease was reported in 1936.[2] Primary hyperparathyroidism in multiple endocrine neoplasia type 2A syndrome (MEN 2A) may present with normo-calcemia or hypercalcemia, with or without renal calculi or patients may have single parathyroid adenoma, multiple adenoma, parathyroid hyperplasia.[3]

Here we reported rare manifestations of primary hyperparathyroidism such as distal renal tubular acidosis due to nephrocalcinosis presenting as hypokalemia paralysis, coexisting Graves's disease with parathyroid adenoma, MEN 2A syndrome presenting as normocalcemic hyperparathyroidism.

Case 1

50 years old male admitted with history of inability to walk due to lower limb weakness, found to have hypokalemia, which improved with potassium correction, and past history of renal calculi. Serum electrolyte report was suggestive of serum sodium 134 mmol/L, serum potassium 2.88 mmol/L, serum calcium 12.8 mg/dl, serum phosphorus 2.6mg/dl, serum intact PTH 876 pg/ml, arterial blood gas analysis was suggestive of pH 7.2, bicarbonate 8 mEq/L, anion gap 9, urine pH 7.5, urinary potassium 41 mmol, transtubular potassium gradient 11 indicating distal renal tubular acidosis. Sestamibi scan showed left inferior parathyroid adenoma, x-ray abdomen had bilateral medullary nephrocalcinosis, [Figure 1] finding was confirmed on USG abdomen-pelvis.

Case 2

50 years old female admitted with palpitations, tremors, weight loss, excessive sweating, bone pain, vomiting, examination revealed thyroid nodule. Investigation showed free T4 5.91 ng/dl, free T3 9.28 pg/ml, TSH 0.0247 mIU/ml, serum calcium 13.5 mg/dl, serum phosphorus 3 mg/dl, serum intact PTH 287.40 pg/ml. USG neck was suggestive of gross enlargement of both lobes of thyroid with left thyroid nodule. Tc 99 sestamibi followed by SPECT CT showed left inferior parathyroid adenoma [Figure 2]. Patient was initiated on carbimazole, propranolol and received intravenous hydration with diuretics, injection zolendronate for hypercalcemia. Serum intact PTH raised to 751 pg/ml after achieving euthyroidism with carbimazole.

Case 3

27 years old male diagnosed with hypertension, plasma free metanephrine (508.3 ng/L) and normetanephrine (3514 ng/L) were raised suggestive of pheochromocytoma, underwent right sided adrenalectomy one year back, serum calcium 9.5mg/dl, serum phosphorus 3.5 mg/dl, serum intact PTH 148.6 pg/ml,24 hour urinary calcium 160 mg/24 hours. After one year patient presented with right side abdominal pain, diagnosed with right sided renal calculi, pyelolithotomy with DJ stenting was done. Serum calcium 10.1 mg/dl, serum phosphorus 2.8 mg/dl, intact PTH 90.8 pg/ml, serum calcitonin 39.2 pg/ml. RET Cys 634 Arg mutation [Figure 3] was positive. Patient underwent total thyroidectomy with parathyroid resection, histopathology revealed left inferior parathyroid adenoma.

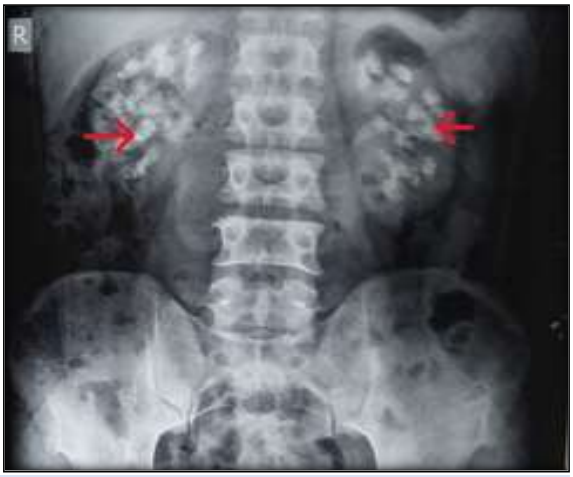

Figure 1: X-ray abdomen suggestive of bilateral nephrocalcinosis

Figure 2: asterisk showing left inferior parathyroid adenoma

Figure 3: RET Mutation

DISCUSSION

In PHPT, longer disease duration of disease may lead to medullary nephrocalcinosis and subsequent distal renal tubular dysfunction. Distal RTA is reported in 10% to 20% of cases of hypercalciuric nephrolithiasis secondary to hyperparathyroidism.[4] Renal tubular damage secondary to hypercalciuria, excess PTH, or a combination of these mechanisms may affect renal tubular epithelium, resulting in damage to the integrity of ion channels and subsequently leading to defect in the urinary acidification mechanisms.[5] Distal RTA is characterized by defect in the generation and maintenance of a hydrogen ion gradient and nephrolithiasis, that differentiate it from proximal RTA. Complete resolution of the distal RTA may occur after parathyroidectomy as shown by the case series by Muthukrishnan et al.[1]

The prevalence of primary hyperparathyroidism is higher in patients with thyroid disease as compared to the general population. Vice versa, the incidence of thyroid abnormalities in patients with primary

hyperparathyroidism ranges from 16.6% to 84.3%.[6] According to a retrospective study, the prevalence of coincidental hyperparathyroidism in patients diagnosed with hyperthyroidism was 13.5%.[7] The exact mechanism of coexistent hyperparathyroidism and hyperthyroidism is still not known. Genetic factor, growth factor, serum calcium may be involved in causation of coexistence of two conditions, some researchers postulated that the occurrence of this association is just a coincidence.[8] A case cohort study involving 21 cases with Graves' disease who developed parathyroid adenoma, where an increased occurrence of parathyroid adenoma might be linked to RAI treatment in Graves' disease with a mean latency period of 26.2 years.[9]

Diagnosis, treatment and follow-up of concomitant Graves' disease and hyperparathyroidism may represent a considerable challenge. Hyperthyroidism leads to to increased osteoclastic activity and bone turnover leading to asymptomatic hypercalcemia.Hyperparathyroidism is typically associated with hypercalcemia and hypophosphatemia, but coexisting Graves's disease masks hypophosphatemia leading to normal phosphorus with normal serum PTH levels,until treatment of Graves' disease reduces thyroid hormone synthesis.Treatment of thyrotoxicosis leads to reduction in osteoclastic activity which results in reduction in serum calcium levels,which further stimulates parathyroid adenoma tissue, which is regulated at higher than normal calcium set point, to increase its activity. This will result in unmasking of hyperparathyroidism by detection of high PTH levels along with low levels of phosphorus and normocalcemia.[10]

Tc 99-MIBI scan may fail to detect parathyroid adenoma in coexisting untreated Graves's disease patients on initial presentation, this can be explained by the excessive absorption of Tc 99 by the hyper-functioning thyroid gland, which completely covers the parathyroid glands. After remission of thyrotoxicosis, the 99mTc-MIBI scintigraphy may show increased uptake by parathyroid adenoma.Treatment for coexisting Graves' disease with hyperparathyroidism is combined near-total thyroidectomy and parathyroidectomy.[11]

Raue F et al. reported that in cohort of 67 patients diagnosed with MEN2A, 84% patients were asymptomatic ,15% had renal calculi. Almost 69% patients had hypercalcemia,16% patients had normal calcium. On histopathological examination 54% had single adenoma,39% patients had parathyroid hyperplasia.[3] Pheochromocytoma, itself may lead to hypercalcaemia in the absence of primary hyperparathyroidism by catecholamine-mediated stimulation of PTH secretion or through production of parathyroid hormone-related peptide.[12] Most of the cases with MEN 2A asssociated hyperparathyroidism have milder disease, with serum calcium levels below 3 mmol/l and without renal manifestation. These patients could be classified as asymptomatic according to the NIH consensus development conference regarding the diagnosis and management of asymptomatic primary hyperparathyroidism.[13]

Normocalcemic hyperparathyroidism is defined by persistently increased serum PTH levels in the setting of normal albumin adjusted and ionized serum calcium, after exclusion of secondary causes of PTH elevation.The consensus statement from the Fourth International Workshop recommend that these laboratory findings should be confirmed at least on two occasions over period of at least 3 to 6 months.The medical conditions or comorbidities must be ruled out to confirm the diagnosis of normocalcemic hyperparathyroidism are as follows: vitamin D deficiency ; insufficient calcium intake or calcium malabsorption; chronic kidney disease; medications such as loop diuretics, thiazide diuretics, lithium, bisphosphonates, or denosumab; and idiopathic hypercalciuria with or without nephrolithiasis.[14]

The most widely accepted hypothesis is that normocalcemic hyperparathyroidism may represent an early or milder form of classical primary hyperparathyroidism. Another hypothesis is that production of PTH by patients with normocalcemic hyperparathyroidism may be lower as compared with that is seen in patients with primary hyperparathyroidism. One study suggested that normal serum calcium in normocalcemic hyperparathyroidism may be due to relatively lower secretion of PTH in these patients.[15] According to literature the prevalence of normocalcemic hyperparathyroidism is variable and it varies between 0.1% and 8.9%. The data is sparse and inconclusive on the natural history of normocalcemic hyperparathyroidism. Some studies show progression of normocalcemia to hypercalcemia, but others do not report same.[16]

CONCLUSION

Clinicians should recognize these rare manifestations of PHPT to avoid delayed diagnosis and treatment. Early identification of atypical presentations, appropriate biochemical evaluation, targeted imaging, and timely surgical intervention can significantly improve patient outcomes and prevent long-term complications.

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