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Case Report

Deciphering The Cause of Hypercalcemia: A Case Report

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ABSTRACT

Multiple endocrine neoplasia type 1 (MEN 1) is a rare, autosomal dominant inherited syndrome. In the present report such a case has been described who presented with the classical clinical, biochemical and radiological findings of MEN 1 syndrome without any familial history, which accounts for this rare report. A female patient, in her thirties presented with fragility fracture of left lower limb. Clinical biochemical investigations revealed hypercalcemia with slightly low phosphate and 25-OH-Vitamin D levels; and elevated alkaline phosphatase and parathyroid hormone levels. Her radiological investigations revealed parathyroid adenoma and bilateral renal medullary nephrocalcinosis. In this case, work-up for hypercalcemia led us to the diagnosis of MEN 1 syndrome. As hypercalcemia is a potentially life-threatening condition and patients might not have any symptoms, the etiological diagnosis should always be sought in order to get better prognosis for the patient.

INTRODUCTION

Miscellaneous causes like Milk-alkali syndrome, prolonged immobilization, parenteral nutrition, adrenal insufficiency, pheochromocytoma etc have been reported as causes for hypercalcemia. One of the rare causes of life threatening hypercalcemia is multiple endocrine neoplasia (MEN). MEN is found with a prevalence of almost 2 per 100,000 among all age groups without any gender bias [1-2]. This disorder is inherited as an autosomal dominant neoplastic and is due to the mutation of the MEN1 gene that functions as a tumor suppressor gene in its normal unmutated state. In healthy condition the MEN1 gene codes for its cognate protein MEN1 that brings out the tumor suppressor effects by promoting DNA repair by homologous recombination mechanism[3]. It is characterized by a predisposition to multiple endocrine and nonendocrine tumors. The major biochemical change in this syndrome is hypercalcemia while the prominent clinical manifestations are hyperplasia, tumors of parathyroid gland along with neoplastic lesions in the enteropancreatic and anterior pituitary areas. However, in addition to these features, neoplastic lesions in forms of carcinoid tumors of intestine, bronchial tissues, thymic tissues, enterochromaffin cells of the stomach, tumors of the adrenocortical glands and phrochromocytoma have been found to be associated with MEN[4]. Familial form of this syndrome is common (90%). Non familial form, although rare, occurs in around 10 % of cases which have de novo germline MEN 1 mutations [5]. Since in our case there is no positive family history for MEN syndrome, it falls into the rare type of non-familial form. This case reporting is based on an incidental association of persistent hypercalcemia with a non familial form of MEN.

Methodology:

Case description:

In our clinical chemistry lab we observed persistent hypercalcemia in a 36 years old female patient over a period of 10 days. Her serum phosphate level was in lower normal range along with elevated alkaline phosphatase enzyme. Parathyroid hormone (PTH) level was raised along with low 25-OH-Vit D levels. Thyroid function tests, anterior pituitary hormones, ACTH, cortisol and estradiol were within normal reference range. Urinary catecholamines were within normal range.

Review of her history revealed that she had presented with chief complaints of fragility fracture of left lower limb which were sustained while getting up from a chair. She had bilateral deep-seated leg pain since one year with occasional pain in the back. There was no history of similar pain anywhere in the body. She had decreased appetite for 3months. She had constipation for one year. There was no history of intake of Calcium and Vitamin D supplements. She had no history of fractures in the past. There was no significant menstrual history. None of her family members had history of renal stones or neck surgery. Her general physical examination revealed pallor.

On studying her case history for clinical correlation, we observed parathyroid adenoma and bilateral renal medullary nephrocalcinosis in the radiological investigation reports. Bone biopsy was also done which revealed giant cell lesion with numerous osteoclast type giant cells with fibroblast proliferation.

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In view of persistent hypercalcemia, Inj calcitonin 200 mg TDS had been given but hypercalcemia persisted. She had underwent open reduction and internal fixation with nails (ORIF) for the tibial fracture diagnosed in her left lower limb. In view of parathyroid adenoma, subtotal parathyroidectomy was done.

Results:
Persistent hypercalcemia over a period of 10 days along with raised Alkaline phosphatase (ALP) levels was observed in the patient's serum sample in our clinical chemistry laboratory for estimation of routine biochemistry analytes and found (Table 1).

Table 1: Study parameters levels for consecutive 13 days.

Parameter	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**
Ionized Calcium (millimol/L) [1.1-1.4 millimol/L]	-	2.12	1.9	-	-	-	-	-	-	1.87	-	1.74	1.2
Total Calcium (mg/dl) [8.1-10.4 mg/dl]	14.9	15	12	12.3	11	12.2	12.4	12.7	12.4	-	13.6	-	-
Corrected Calcium(millimol/L)	-	4.1	3.6	-	-	-	-	-	-	3.6	-	3.3	2.5
Phosphate(mg/dL) [2.5-3.5 mg/dL]	2	2.1	1.4	1.8	1.3	2	2.1	1.5	2.2	-	2.3	-	-
ALP (IU/L) [240-840 IU]	870	958	851	851	681	930	984	900	904	-	1289	-	-
Intact PTH (pg/mL) [15-68.3 Pg/ml]	1090	-	714	-	-	-	-	-	-	-	-	-	23. 37
25-OH-Vit D (ng/mL) [25-80 ng/mL]	16.7	-	8.5	-	-	-	-	-	-	-	-	-	20

Table 1 shows the patient values for calcium, phosphate, ALP, PTH and 25-(OH)-Vitamin D on various days after admission to the hospital.

Table 2 shows values of various analytes that were measured as part of initial work-up for diagnosis for the patient.

Parameter	**Test value**	**Normal range**
T_4 (µg/dL)	7.34	5.1-14.1
TSH (µIU/mL)	1.92	0.27-4.2
FSH (mIU/mL)	3.66	3.5-12.5
LH (IU/L)	7.48	2.4-12.6
GH (µg/mL)	0.48	0.06-6.88
IGF 1 (µg/mL)	168	90-249
PRL (ng/mL)	4.42	6-29.9
ACTH (pg/mL)	15.15	7.2-63.3
Cortisol (mcg/dL)	9.79	5-23
Testosterone (ng/mL)	<0.025	0.084-0.481
DHEA-S (µg/dL)	22.50	60.9-337
Estradiol (pg/mL)	67.81	30-400

All these analytes were found to be within normal reference range.

Table 3 shows the patient values for serum calcium, phosphate, ALP, PTH and 25-(OH)-Vitamin D on various days after undergoing subtotal parathyroidectomy surgery in the hospital.

Parameter	Post op Day 1	Post op Day 3	Post op Day 4	Post op Day 5	Post op Day 6	Post op Day 7	Post op Day 8	Post op Day 9	Post op Day 10
Ionized Calcium (millimol/L) [1.1-1.4 millimol/L]	-	-	1.2	-	-	-	-	1.09	-
Total Calcium (mg/dL) [8.1-10.4 mg/dL]	10.9	8.4	7.2	9.9	9.1	6.8	6.3	-	7.4
Corrected Calcium(millimol/L	-	-	2.5	-	-	-	-	-	-
Phosphate(mg/dL) [2.5-3.5 mg/dL]	2.0	2.1	2.7	2.8	2.6	2.9	2.7	-	3.4
ALP (IU/L) [240-840 IU]	885	1017	1162	1360	1365	1653	1673		1948
Intact PTH (pg/mL) [15-68.3 pg/mL]	-	-	23.37	-	-	-	-	-	-
25-OH-Vit D (ng/mL) [25-80 ng/mL]	-	-	20	-	-	-	-	-	--

Values for serum calcium and PTH were seen to lower down after surgery.

Discussion:

We received the patient's serum sample in our clinical chemistry laboratory for estimation of routine biochemistry analytes and found persistent hypercalcemia over a period of 10 days along with raised Alkaline phosphatase (ALP) levels (Table 1). Total Calcium was measured using "o-cresolphthalein direct colorimetric" method on Roche/Hitachi MODULAR D System. We studied the case in detail to establish the cause of hypercalcemia in this patient.

Hypercalcemia can be parathyroid mediated or non-parathyroid mediated. Parathyroid mediated causes include Primary hyperparathyroidism, tertiary hyperparathyroidism due to renal failure, familial benign hypocalciuric hypercalcemia, Multiple endocrine neoplasia syndromes. Non-parathyroid mediated causes include hypercalcemia of malignancy, Vitamin D intoxication, chronic granulomatous disorders. Some medications like thiazide diuretics, Lithium, Vitamin A toxicity, theophylline toxicity also cause hypercalcemia. Miscellaneous causes like Milk-alkali syndrome, prolonged immobilization, parenteral nutrition, adrenal insufficiency, pheochromocytoma also have been reported as causes for hypercalcemia **[1]**. In our case, thorough clinical history, baseline investigation work up and general examination ruled out non parathyroid mediated causes of hypercalcemia. Her medication history did not reveal anything contributing to hypercalcemia. Patient's parathyroid hormone (PTH) was raised, suggestive of hyperparathyroidism. Radiological investigations also revealed parathyroid adenoma thereby confirming parathyroid mediated cause for hypercalcemia. PTH causes hypercalcemia directly by increased bone resorption, stimulation of calcium reabsorption in the distal tubule of kidney and indirectly by calcitriol mediated increased intestinal calcium absorption. Her kidney function tests were normal, helping to rule out renal failure and in turn tertiary hyperparathyroidism. Therefore, primary hyperparathyroidism was confirmed as cause of hypercalcemia. This also explains the fragility fracture which patient had sustained. As increased PTH leads to bone resorption, her bone became more fragile and prone to fracture. The raised serum ALP levels were due to this fragility fracture in tibia.

Radiological investigations also revealed pancreatic tumor and adrenal tumor which were nonfunctional. No biochemical or radiological evidence of pituitary tumors were found (Table 2). In our case, diagnosis of multiple endocrine neoplasia type 1 (MEN 1) was made based on biochemical and radiological evidence.

MEN 1 diagnosis can be made if one of the following conditions are met **[2]**:

a) Presence of at least two of the following primary MEN1-associated endocrine tumors (*i.e.*, parathyroid adenoma, enteropancreatic tumor, and pituitary adenoma).

b) Any first degree relative of the patient must have at least one MEN1-associated tumor leading to a clinical diagnosis of MEN1.

c) Presence of a *MEN1* mutation in an individual's germline irrespective of presence of any symptoms or biochemical or radiological evidence of MEN1.

Among all adenomas, prathyroid adenomas are the most common frequently reported endocrinal tumors in MEN 1 (Prevalance- 95%) **[6]**. The most common initial manifestation is hypercalcemia (found on laboratory investigation) without pronounced systemic symptoms. Only 25% of these patients have evidence of nephrolithiasis or nephrocalcinosis due to hypercalcemia **[2]**. Our patient had manifestation of hypercalcemia with nephrocalcinosis.

Surgery is the preferred and most effective treatment for parathyroid tumors. Subtotal parathyroidectomy (removal of three and one-half gland) is preferred as it avoids permanent hypoparathyroidism and reduces the period of temporary postsurgical hypocalcaemia **[7]**. In our case subtotal parathyroidectomy was done. But in spite of an effective surgery with a successful subtotal parathyroidectomy in MEN1, a late recurrence of hyper-parathyroidism frequently occurs which may be as high as 50% after 8-12 years after the intervention. Moreover, this tendency of recurrence increases in direct association with the post surgical time period. Hence it is strongly advised to assess the serum calcium and parathyroid hormone levels at regular intervals in the post surgical period**[2]**.However, in spite of best efforts including all recent advances in the diagnostic and therapeutic approach, with a mean age of death of 55–60 years the life expectancy remains quite low in patients with this syndrome compared to the rest of the population, **[9, 10]**. Furthermore, delayed MEN1 diagnosis has been associated with potential harm to patients. Since hypercalcemia is mostly the first manifestation in case of MEN1 syndrome, laboratory evaluation of serum calcium and parathyroid hormone level can be very crucial in early diagnosis. The cause of hypercalcemia should be investigated thoroughly by the laboratory physician as well as the clinician. Cases of hypercalcemia should be followed up by checking parathyroid hormone levels to rule out hyperparathyroidism.

Conclusion:

Most of the MEN1 cases present with no significant symptoms and hypercalcemia is an incidental laboratory finding in most of the cases. But delayed diagnosis of MEN1 syndrome is associated with severe morbidity and in some cases even mortality. As hypercalcemia may sometimes give rise to a potentially life-threatening condition without any marked symptoms, this condition merits significant attention for an early diagnosis and management and to have the most beneficial response, the etiological diagnosis should always be approached keeping all potentially contributing factors in mind which should include the MEN1 which in spite of its rare incidence but potentially dangerous clinical outcome.

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