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General Medicine

A CASE SERIES ON HYPERCALCEMIA

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ABSTRACT Hypercalcemia in adults arises from a myriad of underlying causes. Etiology of hypercalcemia varies from causes like Vitamin D toxicity to hyperparathyroidism, hyperthyroidism, chronic kidney disease, granulomatous diseases, and malignant diseases .Though not an uncommon metabolic problem, hypercalcemia can easily be missed due to the diverse clinical presentations. Primary hyperparathyroidism and malignancy are the most common causes, accounting for 90% of the cases. Clinical manifestation varies depending on the ionized calcium levels. Symptoms manifest when calcium levels exceed 12 mg/dl. We report four different cases that illustrate the need for a focused workup of hypercalcemia. Routine hypercalcemia workup includes serum Parathormone (PTH), Vitamin D, ionized calcium, phosphorus, magnesium, alkaline phosphatase levels, renal functions, and urinary calcium-creatinine ratio. Prognosis depends on the cause of hypercalcemia. The clinical diagnosis needs a high index of suspicion. Definitive management requires focused workup for etiological diagnosis and treatment of underlying cause. Treatment for hypercalcemia is required in all symptomatic patients or if the calcium level exceeds more than 15 mg/dL, even if asymptomatic. Immediate management includes restoring intravascular volume and promoting diuresis. Calcitonin, Bisphosphonates and steroids play a role in medical management. For patient's refractory to medical treatment, hemodialysis is required.

KEYWORDS : Hypercalcemia, hyperparathyroidism, hyperthyroidism, Parathormone, Vitamin D.

Introduction:

The prevalence of hypercalcemia in the general population is approximately 1% to 2% [1]. Etiology of hypercalcemia varies from causes like Vitamin D toxicity to hyperparathyroidism, hyperthyroidism, chronic kidney disease, granulomatous diseases, and malignant diseases [2]. Primary hyperparathyroidism and malignancy are the most common causes among these, accounting for 90% of the cases [3, 4].Though, not an uncommon metabolic problem, hypercalcemia can easily be missed and the diagnosis needs a high index of clinical suspicion. We report four different cases that illustrate the need for a focused workup of hypercalcemia.

Case Presentation

CASE 1: 61-year-old male presented with altered sensorium and anorexia. Clinical examination revealed an emaciated patient with dry skin. He was drowsy and had a pulse rate was 110 beats per minute. The rest of the clinical examination was unremarkable. He got admitted to the Intensive care unit. Neuroimaging done was normal and an electrocardiogram performed showed sinus tachycardia. Initial blood investigations revealed normal hemogram, renal and liver functions. Investigations performed to rule out metabolic causes of altered sensorium revealed hypercalcemia. Serum sodium, Potassium and Magnesium levels were normal. Workup done for hypercalcemia showed normal parathormone, Vitamin D, and cortisol levels. A thyroid function test was done given persistent tachycardia and hypercalcemia revealed a very low TSH value with elevated Free T3 and free T4 levels. Investigations suggested thyrotoxicosis. Table 1 depicts the investigations of case 1. Burch Wartowsky's score was calculated to know the likelihood of thyroid storm. [5] The score is a quantitative diagnostic tool based on thermoregulatory, gastrointestinal, cardiovascular, and central nervous system dysfunctions. A score above 45 suggests thyroid storm, 25-44 suggests impending thyroid storm and < 25 unlikely to represent thyroid storm. The score calculated in the patient was 20. Thus, a clinical diagnosis of thyrotoxicosis with secondary hypercalcemia was arrived upon. Hypercalcemia was corrected with intravenous fluids and diuretics and he was initiated on anti-thyroid medications. He responded to treatment and calcium levels normalized. Additional workup for thyrotoxicosis with radioiodine uptake scan done was suggestive of Graves's disease.

Table 1: Investigations of Case 1

Test	Result	Normal range
Hemoglobin	12 g/dL	13.2-16.6 g/dL
ESR	40 mm/hr	0-30 mm/hr
Calcium	12.5 mg/dL	8.6-10.6 mg/dL
Phosphorous	3.1 mg/dL	2.5-4.5 mg/dL
Magnesium	1.9 mg/dL	1.7 to 2.2 mg/dl
Sodium	139 mEq/L	135-145 mEq/L
Albumin	3.4 gm/dL	3.5-5 gm/dL
TSH	<0.01micro IU/ml	0.5-5.5 micro IU/ml
Free t4	57pmol/L	12-23 pmol/L
Free t3	9.6 pg/dL	3.5-6.5 pmol/L
25 OH Vit D	40 ng/mL	30-100 ng/mL
i-PTH	<4.0 pg/mL	9.2-44.6 pg/mL
Serum Cortisol 8.00 A.M	22 mcg/dL	5-23 mcg/dL
Urine calcium/creatinine ratio	120	< 0.14

(ESR: Erythrocyte sedimentation rate, TSH: Thyroid stimulating hormone, i-PTH: Intact Parathormone, 25 OH Vit D- 25 hydroxy Vitamin D.)

CASE 2: 95-year-old female presented with a decreased response, back pain, anorexia, and weight loss. Routine investigations revealed anemia with raised ESR, hypoalbuminemia, elevated globulin, hypercalcemia and hyperuricemia. A peripheral blood smear revealed microcytic hypochromic anemia with no atypical cells. The clinical and laboratory findings pointed towards the possibility of paraproteinemia. X-ray pelvis showed two well-defined lytic lesions. Serum electrophoresis revealed an M band. She was diagnosed with Multiple myeloma-induced hypercalcemia. Table -2 depicts the summary of necessary investigations. Hypercalcemia got corrected by IV hydration, bisphosphonates, and other supportive measures. The patient became symptomatically better and is now under follow up for multiple myeloma.

Table 2: Investigations of Case 2

Test	Result	Normal range
Hemogloblin	5.7g/dL	13.2-16.6g/dL

ESR	64 mm/hr	0-30mm/hr
Calcium	12.1 mg/dL	8.6-10.6 mg/dL
Phosphorous	4 mg/dL	2.5-4.5 mg/dL
Magnesium	2.2 mg/dl	1.7 to 2.2mg/dl
Sodium	142 mEq/L	135-145 mEq/L
Potassium	5.0 mEq/L	3.6-5.2 mEq/L
Albumin	2.8 gm/dL	3.5-5 gm/dL
Globulin	4 g/dL	2.0-3.5 g/dL
Uric acid	8.5 mg/dL	3.5-7.2 mg/dL
i-PTH	8 pg/mL	9.2-44.6 pg/mL
TSH	3.5micro IU/ml	0.5-5.5 micro IU/ml
Urine calcium creatinine ratio	96	< 0.14
Serum electrophoresis	Showed M band in the gamma region.	

(ESR: Erythrocyte sedimentation rate, TSH: Thyroid stimulating hormone, i-PTH: Intact Parathormone)

CASE 3: 58-year-old male presented with complaints of fever, tiredness, anorexia, pain, and swelling in his left inguinal region. On Clinical examination, patient was dehydrated, and disoriented, and had left lower leg cellulites with enlarged tender left inguinal lymph nodes. He had polyuria with 24 hour urine excretion around 4-6 L/day. Baseline Investigations revealed leukocytosis, thrombocytopenia altered liver function and renal function tests. Neuroimaging done was normal. He had hypernatremia and hypercalcemia. Ultrasound of the abdomen showed nephrocalcinosis and ultrasound neck was normal. Hypercalcemia workup revealed raised PTH levels with grossly elevated urine calcium creatinine ratio. High serum osmolality and low urine osmolality in the background of polyuria, possibility of nephrogenic diabetes insipidus secondary to hypercalcemia was considered. Blood and pus culture and sensitivity showed polymicrobial growth of Enterobacter species. The summary of investigations is depicted in Table 3. Antibiotics optimized following the culture reports. He was diagnosed with polymicrobial sepsis, primary hyperparathyroidism and hypercalcemia - induced nephrogenic diabetes insipidus. Technetium 99 (Tc 99) MIBI scan of the neck was planned but couldn't be done as the patient was sick. Hypercalcemia corrected with adequate hydration and Inj. Calcitonin. Despite treatment, he succumbed to the illness.

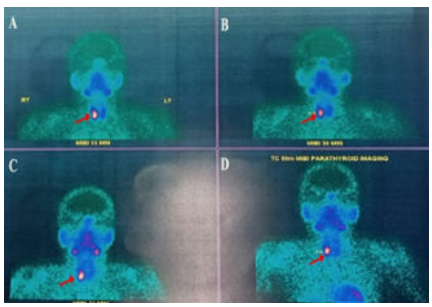
Table 3: Investigations of Case 3

Test	Result	Normal range
Hemoglobin	9.4 g/dL	13.2-16.6g/dL
ESR	90 mm/hr	0-30 mm/hr
Leucocyte count	27,000 cells/mcL	4500-11000 cells/mcL
Platelet count	80,000cells /mcL	150,000-400,000 cells /mcL
Sodium	156 mEq/L	135-145mEq/L
Potassium	3.5 mEq/L	3.6-5.2 mEq/L
Calcium	15.5 mg/dL	8.6-10.6 mg/dL
Phosphorous	3.61 mg/dL	2.5-4.5 mg/dL
Magnesium	1.8 mg/dL	1.7-2.2mg/dL
Uric acid	8 mg/dL	3.5-7.2 mg/dL
Urea	150 mg/dl	6-24 mg/dL
Serum Creatinine	2.4g/dl	0.7-1.3 mg/dL
Total Bilirubin	4.3 mg/dL	0.1-1.2 mg/dL
Direct bilirubin	2.6 mg/dL	< 0.3 mg/dL
Albumin	2.4 gm/dL	3.5-5 gm/dL
Aspartate transaminase	151 U/L	8-33 U/L
Alanine transaminase	99 U/L	4-36 U/L
Alkaline Phosphatase	120 IU/L	44-147 1U/L
i-PTH	79 pg/mL	9.2-44.6pg/mL
25 OH Vit D	32 ng/mL	30-100 ng/mL
Serum Cortisol 8.00 A.M	32 mcg/dL	5-23 mcg/dL
TSH	2.3micro IU/ml	0.5-5.5 micro IU/ml
Urine calcium creatinine ratio	903	<0.14
Spot Urine Sodium	16mEq/L	>20mEq/L
Urine Osmolality	140 mmol/L	50-1200 mOsm/kg
Serum Osmolality	360 mmol/L	275-295 mOsm/kg
Procalcitonin	64 ng/mL	less than 0.1 ng/mL
Blood culture	Enterococcus faecalis	No growth
Pus culture	Enterobacter species	No growth

(ESR: Erythrocyte sedimentation rate, TSH: Thyroid stimulating hormone, i-PTH: Intact parathormone)

CASE 4: 48-year-old female presented with complaints of pain and swelling of the right breast, generalized tiredness, and easy fatigability. Clinical examination revealed a firm mass over lower medial quadrant of the right breast. The mammogram revealed a hypoechoic lesion of BIRADS III grade in the right lower quadrant. Fine-needle aspiration done from the breast lesion showed collection of ductal epithelial cells with no atypia. USG abdomen was done as a part of general check up and revealed left renal calculus. While investigating the causes of renal calculi, she was found to have hypercalcemia with normal phosphorus levels. Hypercalcemia workup revealed abnormally high normal parathyroid hormone levels with low vitamin D levels. The urine calcium creatinine ratio was high. Thus, she was diagnosed with PTH-dependent hypercalcemia. Ultrasonography of the neck revealed hypoechoic lesion in the posteroinferior pole to right thyroid with multiple nodules over right thyroid gland. Technetium 99 (Tc 99) MIBI scan of the neck showed increased uptake in the right inferior parathyroid gland suggestive of adenoma as shown in Figures 1A -1D. Summary of the investigations are given in table 4.Based on the workup, she was diagnosed with primary hyperparathyroidism secondary to right inferior parathyroid adenoma. The patient underwent Right hemithyroidectomy with right parathyroid adenoidectomy .She is doing well and is on follow up.

Figure 1A- 1D: Tc 99 uptake by right inferior parathyroid adenoma



(Arrows show the right inferior parathyroid gland. Figure 1A- uptake at 15 minutes ,Figure 1B- uptake at 15 minutes ,Figure 1C- uptake at 30 minutes, Figure 1D- uptake at 45 minutes)

Table 4: Investigations of Case 4

Test	Result	Normal range
Hemoglobin	12.5 g/dL	13.2-16.6 g/dL
ESR	26 mm/hr	0-30 mm/hr
Calcium	12.4mg/dl	8.6-10.6 mg/dL
Phosphorous	2.5mg/dL	2.5-4.5 mg/dL
Magnesium	2.4 mg/dL	1.7 to 2.2 mg/dL
Potassium	4.1 mEq/L	3.6-5.2 mEq/L
Uric Acid	6.2 mg/dL	3.5-7.2 mg/dL
Sodium	138mEq/L	135-145 mEq/L
Albumin	4.3 gm/dL	3.5-5 gm/dL
i-PTH	39 pg/mL	9.2-44.6 pg/mL
25 OH Vit D	< 8.1ng/mL	30-100 ng/mL
TSH	2.5 micro IU/mL	0.5-5.5 micro IU/mL
Free t3	280 pg/dL	130-450 pg/dL
Free t4	4.3 ng/dL	0.9- 2.3 ng/dL
Urine calcium creatinine ratio	506	< 0.14

Mammogram	Hypoechoic lesion of BIRADS III in the right lower quadrant.
FNAC from breast	Paucicellular smears with cluster of ductal epithelial cells
Ultrasonography of Abdomen	Fatty hepatomegaly, with non-obstructing left renal calculus
Ultrasonography of neck	Three nodules in the right lobe of thyroid ACR TR4. A hypoechoic lesion in the posteroinferior pole to right thyroid suggestive of parathyroid adenoma
Tc 99 Sestamibi scan	Right inferior pole parathyroid adenoma

(ESR: Erythrocyte sedimentation rate, TSH: Thyroid stimulating hormone, 25 OH Vit D- 25 hydroxy Vitamin D, i-PTH: Intact Parathormone, FNAC- Fine needle aspiration cytology, Tc 99 - Technetium 99)

Discussion:

The normal serum calcium level ranges from 8.8 mg/dL-10.8 mg/dL. Symptoms manifest when calcium levels exceed 12 mg/dl. The severity of the symptoms depends on the rapidity of the onset and the calcium concentration [6].The classical presentations irrespective of the etiology are summarized as "groans, bones, stones, moans, thrones and psychic overtones" [7].

Asymptomatic PHPT is detected predominantly on routine biochemical screening [8]. Hyperthyroidism associated hypercalcemic crisis is a very rare presentation. Hypercalcemia attributable to thyrotoxicosis may be due to the effect of thyroid hormone on bone turnover [9]. Multiple myeloma, a cancer of plasma cells, is associated with excessive tumor-induced, osteoclast-mediated bone destruction. Excessive osteolysis plays an important role in the pathogenesis of myeloma induced hypercalcemia [10, 11]. Though the mechanisms of hypercalcemia-induced nephrogenic diabetes insipudus are not clearly understood, it is suggested due to the enhanced activity of enzymes/proteins involved in autophagy, specifically targeting AQP2 for degradation [12].

Routine hypercalcemia workup includes serum Parathormone (PTH), Vitamin D, ionized calcium, phosphorus, magnesium, alkaline phosphatase levels, renal functions, and urinary calcium-creatinine ratio. Hypercalcemia should be confirmed by measuring ionized calcium and should be corrected for hypoalbuminemia. Sensitive and specific immune-chemiluminometric assays should be used to measure intact parathyroid hormone ((i-PTH) [6,8]. A focused workup for etiological diagnosis is required for definitive management.

Hyperparathyroidism is characterized by high calcium, low phosphorous levels, and high i-PTH levels. High serum concentrations of calcidiol are found in patients with hypervitaminosis D, whereas, patients with a granulomatous disease have high calcitriol levels. In patients with hypercalcemia associated with malignancy, the PTH-related peptide levels are elevated [3, 8].

Treatment for hypercalcemia should be initiated in all symptomatic patients and asymptomatic patients if calcium levels are above 15 mg/dL [6].Immediate management includes restoring intravascular volume and promoting diuresis. Loop diuretics are to be used with caution as they may cause paradoxical hypercalcemia due to bone resorption. Calcitonin can be administered but its effects are usually mild. Bisphosphonates are the drugs of choice for hypercalcemia of malignancy as they inhibit osteoclastic activity. Steroids are beneficial or Hypercalcemia associated with excess vitamin D. Primary hyperparathyroidism secondary to adenoma needs surgical intervention for the excision of the tumor. Drugs causing hypercalcemia should be discontinued in drug-induced hypercalcemia For patient's refractory to medical treatment, hemodialysis is required [6, 13].

Conclusion: Hypercalcemia has varied presentations. Though not an uncommon metabolic problem, hypercalcemia can easily be missed. Severity of symptoms depends on the rapidity of onset and the degree of hypercalcemia. High index of clinical suspicion is needed for an early diagnosis. Definitive management requires focused workup for etiological diagnosis and treatment of underlying cause. All symptomatic patients as well as asymptomatic patients with calcium levels above 15 mg/dL should be treated immediately.. Immediate management includes restoring intravascular volume and promoting diuresis. Calcitonin, Bisphosphonates and steroids play a role in medical management. For patient's refractory to medical treatment, hemodialysis is required. Most of the patients are amenable to cure.

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