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Case Report

Vitamin A Induced Hypercalcemia in a Patient with Chronic Renal Failure: A Case Report

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Introduction

Hypercalcemia is a relatively common and serious clinical problem in adults. Vitamin A intoxication secondary to over-the-counter nutritional supplements and from its use in acne treatment has been described. However, there have been very few case reports of chronic A toxicity leading to hypercalcemia. This paper describes a young female with hypercalcemia secondary to chronic vitamin A intoxication.

Case Presentation

This is a 29 year-old female who is known to have a hypertension, chronic kidney disease stage V (no clear etiology, possible chronic glomerulonephritis, serology and autoimmune workup were negative, no renal biopsy was done, planning for renal transplant from living donor – her mother), iron deficiency anemia, and acne vulgairs. She is on the following medications: amlodipine 10 mg, darbepeotein alfa 50 mcg q2wk, calcium-vitamin D 600 mg BID, calcitriol 0.25 mcg, sodium bicarbonate 325 mg BID, ferrous sulfate 47 mg, adapalene-benzoyl peroxide topical, isotretinoin, and doxycycline oral 100 mg (last three medication were prescribed by her dermatologist). Patient is allergic to ibuprofen and mefenamic acid. Patient used to work as a front desk agent at one of the hotel, lives with her friends in UAE, her family lives in her home country – Republic of the Philippines, she is not smoking or drinking alcohol. Family history of hypertension in her father and aunt and kidney failure in her aunt at young age (started on hemodialysis at age of 42 years). Patient presented to emergency department with two days history of epigastric pain, nausea, vomiting, and periorbital edema, and two weeks history of fatigability, bruises, and lower limbs edema. History of chronic headache. No diarrhea or constipation. No cough, chest pain, or hemoptysis. Patient is producing good amount of urine with no urinary symptoms. No skin rash. No facial deviations or limbs weakness. No weight loss, fever, or night sweats. No history of sick contact or recent travel. No family history of hypercalcemia, nephrolithiasis, hyperparathyroidism, thyroid neoplasms, or pituitary tumors. In emergency department, she was afebrile with temperature of 36.6C, respiratory rate of 18 breath per minute, heart rate of 98 beat per minute, blood pressure of 138/83 mmHg, and oxygen saturation of 100% on room air. On examination when she was initially seen in the emergency unit, her weight was 48.70 kg and height 160 cm. She was alert, oriented, and in discomfort complaining of abdominal pain. She was noted to have periorbital edema, bilateral fine crackles on chest examination with bilateral lower limbs pitting edema. Abdominal examination revealed mild generalized abdominal tenderness more in epigastric area. Cardiovascular, and neurological exam were all within normal limits. There was no evidence of thyromegaly, and thyroid gland was non-tender.

Laboratory investigations as shown in Table 1 revealed severe hyponatremia of 119mmol/L, normal potassium level of 4.1mmol/L, hypochloremia of 83mmol/L, creatinine of 1348micromol/L, urea of 40.60mmol/L, bicarbonate 17mmol/L, hypermagnesemia of 1.12mmol/L, hypercalcemia corrected calcium 3.12mmol/L, ionized calcium 1.33mmol/L, hypoalbuminemia of 31g/L, hyperphosphatemia 2.20mmol/L, normal AST 22IU/L (normal range <= 32), normal ALT 12IU/L (normal rage <=33), normal alkaline phosphatase 63IU/L (normal range 35-104), normal total bilirubin 6.4micromol/L (normal rage <=21), amylase and lipase were not measured, serum osmolality 292mOsm/kg, PTH 2.1pmol/L (normal range 1.6 – 6.9pmol/L), vitamin D 25 OH level of 28.2nmol/L, 1,25-Dihydroxyvitamin D <8ng/ml (normal range 18 -78), cortisol level 575nmol/L, normal TSH 1.970mili IU/L, normal free T4 13.7pmol/L, urine osmolality

262mOsm/kg, urine sodium 39mmol/L, urine chloride < 50mmol/L, urine potassium 28.2mmol/L, no leukocytosis or leucopenia white cell count 7.9X109/L, normocytic normochromic anemia (hemoglobin level of 91g/L) with normal RDW, normal coagulation profile, ECG showed normal sinus rhythm with heart rate of 90bpm and normal QT interval, CXR was unremarkable. Patient admitted as a case of fluid overload and uremia secondary to chronic kidney disease stage V, severe acute symptomatic hypervolemia hyponatremia, moderate hypercalcemia, for further management. Patient started on intravenous diuretics, fluid restriction, and calcitonin 200units q12hr. Isotretinoin, doxycycline, and oral calcium supplements discontinued on admission. Repeated labs in the next day showed hypornatremia of 123mmol/L, hypercalcemia corrected calcium 3.01mmol/L, creatinine 1,415micromol/L, urea 40.40mmo/L, bicarbonate 20mmol/L, calcitonin dose increased from 200mg q12hr to 200mg q8hr. Tunnel catheter (right internal jugular vein) inserted in the next day and patient started on haemodialysis, she had three consecutive haemodialysis sessions. Sevelamer added. Repeated labs after dialysis showed hyponatremia of 129mmol/L, hypermagnesemia 1.21mmol/L, hyperphosphatemia 2.42mmol/L, corrected calcium level 2.60mmol/L, PTH 8.2pmol/L. Patient's symptoms resolved and discharged home in a good condition. The patient was following up regularly in nephrology clinic; she was doing well and has no complaints, calcium supplements (calcium lactate 500mg BID and alfacalcidol 1mcg) restarted, patient avoided vitamin A supplements.

Labs	Results	Labs	Results
Sodium	119mmol/L Low	AST	22IU/L (normal range <= 32)
Potassium	4.1mmol/L normal	ALT	12IU/L (normal rage <=33),
Chloride	83mmol/L low	Alkaline phosphatase	63IU/L (normal range 35-104)
Creatinine	1348micromol/L high	Total bilirubin	6.4micromol/L (normal rage <=21)
Urea	40.60mmol/L high	Serum osmolality	292mOsm/kg
bicarbonate	17mmol/L low	PTH	2.1pmol/L (normal range 1.6 – 6.9pmol/L)
Magnesium	1.12mmol/L high	Vitamin D 25 OH	28.2nmol/L
Corrected calcium	3.12mmol/L high	1,25-Dihydroxyvitamin D	<8ng/ml (normal range 18 -78)
Ionized calcium	1.33mmol/L high	Cortisol	575nmol/L normal
Phosphate	2.20mmol/L high	TSH	1.970mili IU/L normal
Hemoglobin	91g/L low	Free T4	13.7pmol/L normal
WCC	7.9X109/L normal	Albumin	31g/L low

Urine			
Labs	Results	Labs	Results
Osmolality	262mOsm/kg	Chloride	< 50mmol/L
Sodium	39mmol/L	Potassium	28.2mmol/L

Table 1: Laboratory results.

Discussion

Hypercalcemia is a relatively common clinical problem in adults. Signs and symptoms of hypercalcemia include polyuria, polydipsia, nephrolithiasis, nephrocalcinosis, distal renal tubular acidosis, acute renal insufficiency, anorexia, nausea, vomiting, constipation, pancreatitis, peptic ulcer disease, muscle weakness, bone pain, fatigue, shortening of the QT interval, bradycardia, and hypertension [1]. Differential diagnosis of hypercalcemia includes primary hyperparathyroidism, secondary and tertiary hyperparathyroidism, malignancy, granulomatous diseases such as tuberculosis, leprosy, histoplasmosis, and sarcoidosis, milk-alkali syndrome, and familial hypocaluric hypercalcemia, medications induced such as calcium, vitamin D and vitamin A supplements [1]. Our patient presented with epigastric pain, nausea, vomiting, and fatigability. Her corrected calcium level was elevated 3.12mmol/L, PTH intact was 2.1pmol/L (normal range 1.6 – 6.9pmol/L), hyperphosphatemia 2.20mmol/L, normal AST 22IU/L (normal range <= 32), normal ALT 12IU/L (normal rage <=33), normal alkaline phosphatase 63IU/L (normal range 35-104), normal total bilirubin 6.4micromol/L (normal rage <=21). Repeated labs after dialysis showed hyponatremia of 129mmol/L, hypermagnesemia 1.21mmol/L, hyperphosphatemia 2.42mmol/L, corrected calcium level 2.60mmol/L, PTH 8.2pmol/L. The most common cause of hypercalcemia are primary hyperparathyroidism in an outpatient setting and malignancy in inpatient setting. Primary hyperparathyroidism occurs when one or more parathyroid glands produce inappropriately high amounts of parathyroid hormone relative to the serum calcium level, causes include adenoma, hyperplasia, and carcinoma. Low normal PTH is most consist with non-PTH mediated hypercalcemia. In our patient, the low 1,25-dihydroxyvitamin D probably reflects a reduced activity of the renal 1-hydroxylase enzyme activity in the face of suppressed PTH; PTH is required for activation of the 1-hydroxylase enzyme. Additionally, our patient has hyperphosphatemia which explained by her underlying renal disease, so primary hyperparathyroidism cannot be excluded. After starting her dialysis, her laboratory investigations were consist of tertiary hyperparathyroidism which occurs when parathyroid hormone production becomes autonomous and levels do not fall once serum calcium is corrected with supplementation of calcium and vitamin D. Secondary hyperparathyroidism a response to hypocalcemia, not a cause of hypercalcemia.

Malignancy such as multiple myeloma and bone metastases should be considered in patient with hypercalcemia that can increase serum calcium by several mechanisms; parathyroid hormone related peptide release, osteolysis, calcitriol-mediated hypercalcemia, and ectopic parathyroid hormone secretions. She was using calcium supplements given the fact that her vitamin D 25 OH level is 28.2nmol/L excludes vitamin D intoxications. She does not have respiratory symptoms such as cough, shortness of breath, or chest pain, and has normal CXR. Additionally, 1,25-Dihydroxyvitamin D was low <8ng/ml (normal range 18 -78) which increased in granulomatous diseases and lymphoma due to increased production of 1.25-OH vitamin D from activated pulmonary macrophages, and increased intestinal absorption of calcium, which in turn increase serum calcium. The patient was using doxycycline, adapalene-benzoyl peroxide topical, and isotretinoin since months for acne vulgairs. Vitamin A is a lipid-soluble compound referred to as retinoic acid, and plays an important role in vision, and bone growth [2]. Vitamin A toxicity can be divided into acute and chronic [2]. Acute form occurs with ingestion of >200mg of single dose of vitamin A, while the chronic form occurs with long-term ingestion of vitamin A doses higher than 10 times the recommended daily allowance [2].The kidneys play an important role in vitamin A metabolism and excretion as shown in Figure 1 [3]. In healthy individuals, dietary vitamin A is converted into retinol (ROH), stored in the liver, and then will be transported into to its target cells by its carrier proteins which are retinol-binding protein-4 (RBP) and transthyretin (TTR). Retinol (ROH) is oxidized to its active form, retinoic acid (RA), and free retinol-binding protein-4 (RBP) is then degraded and filtered by the kidneys [3]. Vitamin A concentrations are increased in chronic renal failure even with ingestion of less than the usual toxic doses and this is because of high circulating levels of retinol, due to a combination of decreased glomerular filtration of the retinol-retinol-binding protein-4 complex, reduced conversion of retinol to retinoic acid (RA), and because of accumulation of retinol-binding protein-4 (RBP) [3]. The prevalence of hypervitaminosis A in chronic kidney disease is not known [3]. Symptoms and signs of hypervitaminosis A include dry skin, nausea, headache, fatigue, irritability, anorexia, liver disease, hepatomegaly, hair loss, alopecia, dyslipidemia and increased cerebrospinal fluid pressure [2]. It is not clear exactly how vitamin A influences bone metabolism, but probably acts on bone by stimulating osteoclastic resorption, or by inhibiting osteoblastic formation [2]. In our case, the patient had worsening of her kidney function over the last year with the use of vitamin A that contributes and increase her serum calcium. There is a study done in children across a wide range of kidney function and found that hypervitaminosis A is present from early stages of chronic kidney disease in children, and is associated with increased dietary vitamin A intake [3]. There is no evidence-based guidelines on vitamin A intake in patients with CKD, therefore vitamin A should be prescribed with caution in patients with impaired renal function [3]. Additionally, the use of some drugs such as tetracycline (doxycycline) increase the risk of vitamin A toxicity [2].

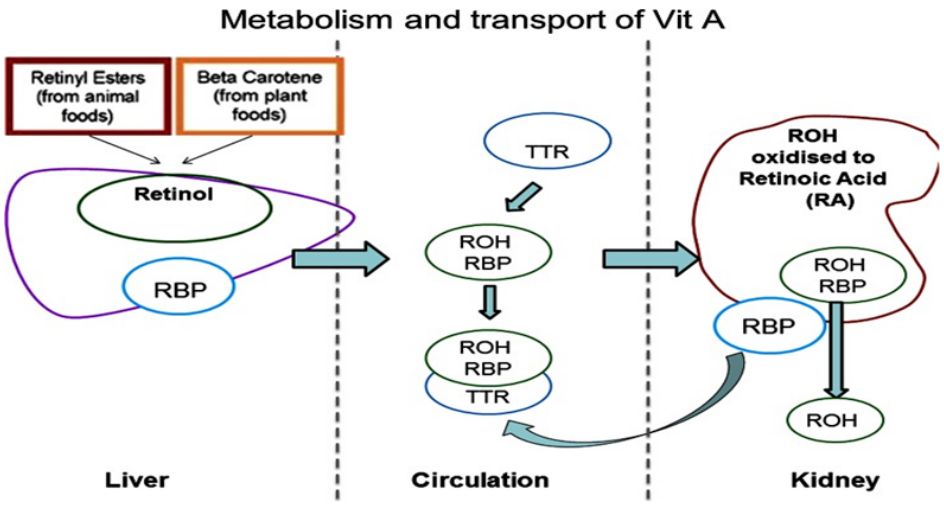

Figure 1: vitamin A metabolism.

Vitamin A induced hypercalcemia reported in four groups; the first group of patients is those who receive ATRA (all-trans retinoic acid) therapy for treatment of acute promyelocytic leukemia, the second group involves hemodialysis patients developing vitamin A toxicity related to consumption of nutritional supplements containing pharmacological doses of vitamin A, the third group includes few case reports describing hypercalcemia in association with massive ingestion of vitamin A, and the last one described a case report of vitamin A toxicity caused by enteral feeding using commercially available tube-feed formula [2]. Serum vitamin A level was not measured in our case. There was a study done in 14 haemodialysis patients who were followed for an average of 8.4 months after stopping oral vitamin A supplements (5,000 U daily), found that there are no change in the mean vitamin A plasma levels. The conclusion of this study is that the vitamin A levels in haemodialysis patients are increased because of an increase in retinol binding protein [5]. Our patient was not taking lithium, teriperatide, thiazide diuretics, and theophylline which can cause hypercalcemia [4]. Milk-alkali syndrome consists of the triad of hypercalcemia, metabolic alkalosis, and acute kidney injury associated with the ingestion of large amount of calcium and absorbable alkali. Our patient is taking calcitriol but she had metabolic acidosis with progressive kidney disease which excludes this syndrome. 15%-20% of patients with hyperthyroidism has mild hypercalcemia due to a thyroid hormone-mediated increase in bone resorption [4]. Our patient had normal TSH and free T4 which excludes hyperthyroidism. She is used to work as a front desk agent at one of the hotel, mobilizing, orally fed, compliant to her renal diet, and has normal cortisol level which can exclude other causes of hypercalcemia such as immobilization, dehydration, parenteral nutrition, and adrenal insufficiency. She does not have the symptoms and signs suggestive of acromegaly and pheochromocytoma. There is no family history of such as symptoms to suggest familial hypocaluric hypercalcemia that caused by inactivating mutations of the calcium sensing receptor (CaSR). Treatment of hypercalcemia depends on the patient's symptoms and level of total albumin-corrected calcium. Patients with asymptomatic or mildly symptomatic hypercalcemia (corrected calcium level < 12mg/dl – 3mmol/L), do not require immediate treatment [4]. However, they advised to maintain adequate hydration by drinking at least six to eight glasses of water per day to minimize the risk of nephrolithiasis, mobilize, and avoid medications that can aggravate hypercalcemia. Symptomatic or asymptomatic patients with moderate hypercalcemia (corrected calcium between 12 and 14 mg/dl – 3 to 3.5mmol/L) should follow the same precautions measures that described in mild hypercalcemia, in addition to saline hydration and bisphosphonates for symptomatic patients. Patients with severe hypercalcemia (corrected calcium level of > 14mg/dl – 3.5mmol/L) either symptomatic or asymptomatic require aggressive therapy with volume expansion with isotonic saline at initial rate of 200-300 ml/hour to maintain urine output at 100 to 150ml/hour, calcitonin 4-8 IU/kg every 6-12 hours for 24-48hours as the patient may develop tachyphlaxis, and bisphosphonates (intravenous zoledronic acid

4mg over 15 minutes or pamidronate 60-90mg over two hours). Other modalities of hypercalcemia therapy include corticosteroids and treatment of underlying disease. Our patient was treated by stopping offending agents such as calcium supplements and vitamin A, calcitonin, and with hemodialysis, which provide improvement in her corrected calcium level [4]. Hydration and bisphosphonates is contraindicated in our case due to fluid overload and renal impairment [4]. Regular follow-up in nephrology clinic with other disease's features exclude the main causes of hypercalcemia includes primary hyperparathyroidism, malignancy, sarcoidosis, and tuberculosis. Based on above explanations, the most likely cause of hypercalcemia in our patient is vitamin A intake.

Conclusion

Vitamin A toxicity is a rare cause of hypercalcemia. The exact mechanism of vitamin A induced hypercalcemia is not well understood but probably acts directly on the bones by stimulating osteoclastic resorption, or by inhibiting osteoblastic formation. The vitamin A levels in haemodialysis patients are increased because of an increase in retinol binding protein, therefore vitamin A should be prescribed with caution in patients with impaired renal function.

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