ORIGINAL ARTICLE

VITAMIN-D TOXICITY AND OTHER NON-MALIGNANT CAUSES OF HYPERCALCEMIA: A RETROSPECTIVE STUDY AT A TERTIARY CARE HOSPITAL IN PAKISTAN

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Background: Hypercalcemia is a common clinical problem; primary hyperparathyroidism and malignancy is commonest causes of hypercalcemia. Aetiology of hypercalcemia are changing, causes that were diseases of the past like Vitamin-D toxicity and milk alkali syndrome are observed more often. Vitamin-D deficiency is an important problem and overzealous replacement of Vitamin-D has been observed, suspected to cause toxicity. **Method:** This was a retrospective review of patients admitted at the Aga Khan University Hospital from January 2008 to December 2013 with hypercalcemia. We reviewed the electronic health records for laboratory and radiological studies, and discharge summaries to establish the cause of hypercalcemia. Patients with solid tumour malignancy were excluded from the analysis. The treatment records and hospital course of patients diagnosed with Vitamin-D toxicity were also reviewed. **Results:** Primary hyperparathyroidism was the most common cause of hypercalcemia comprising 41 (28.2 %) patients. Vitamin-D toxicity was present in 25 (17.3%) and probable Vitamin-D toxicity 11 (7.6 %) inpatients. Vitamin-D toxicity and probable Vitamin-D toxicity together comprised 36 (24.8%) cases. Other causes of hypercalcemia included multiple myeloma 18 (12.4%) patients, tuberculosis 6 (4.1%) patients, chronic kidney disease6 (4.1%) cases, sarcoidosis 4 (2.7%) and lymphoma 3 (2.0%) patients. In 29(20%) patients a cause of hypercalcemia could not be determined and were labelled as undiagnosed cases. **Conclusion:** Vitamin-D toxicity was the second commonest cause of hypercalcemia after primary hyperparathyroidism. Knowledge of the prevalent and emerging causes of hypercalcemia is important for prompt diagnosis and treatment.

Keywords: Vitamin-D toxicity; Hyperparathyroidism; Hypercalcemia

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INTRODUCTION

Hypocalcaemia is a common clinical problem; primary hyperparathyroidism (HPT) and malignancy are commonest causes of hypercalcemia.[1,2] Frequency of hypercalcemia in different disease entities has been described. However recent literature is lacking about frequency of different aetiologies when patient presents primarily with hypercalcemia. Study in the military veteran's population in the United States showed that 54% of the patients had hypercalcemia attributable to causes other than malignant disease or HPT.[3]

Studies in our region are limited to the frequency of hypercalcemia occurring in specific diseases. The spectrum of the aetiology of hypercalcemia may be changing and the causes that were diseases of the past like Vitamin-D toxicity (VDT) and milk alkali syndrome; are observed more often. The only study highlighting the frequency of hypercalcemia in Pakistan is limited to patients with multiple myeloma.[4]

Vitamin-D deficiency (VDD) has resurfaced as an important public health problem; and at the same time overzealous replacement of Vitamin-D has also been observed. Intramuscular Vitamin-D preparations, containing 200,000 and 600,000 IU of Vitamin-D3 are commonly used in Pakistan. Guidelines on these vitamin preparations are lacking. Practices among physicians vary widely, conservative being using 600,000 IU IM or orally every 3 months to very aggressive regimen of 600,000 IU weekly for up to 12 weeks.[5] Review of laboratory data from our centre is suggesting shifting of Vitamin-D deficiency to hypervitaminosis D and toxicity.[6] Sporadic cases of VDT have been noticed by the physician community. However, there is no published literature to evaluate the magnitude of VDT. Bansal *et al* from India reported a case of Vitamin-D toxicity in a patient who had received 10 injections of Vitamin-D3, 600,000IU after the knee surgery.[7] Hypercalcemia has also been reported because of excess ingestion of Vitamin-D in dietary supplements.[8,10] In two cases, the amounts of Vitamin-D found in vitamin preparations were much higher than listed by the manufacturer.[9,10]

Hypercalcemia presents as a diagnostic challenge except in patients with solid tumour

malignancy where it is a late finding and underlying disease is often known.[11] Knowledge of the commonly occurring causes will help in reaching the diagnosis promptly and in a cost-effective manner. It can identify preventable causes and may demand change in replacement practices of Vitamin-D.

MATERIAL AND METHODS

This study was a retrospective analysis examining the causes of hypercalcemia in patients without solid tumour malignancy. A list of patients, admitted with hypercalcemia from January 2008 to December 2013 at the Aga Khan University Hospital (AKUH) was generated by Health Information Management Systems department. Patients admitted under the care of an oncologist were excluded from the search. The study was approved by the ethics review committee of AKUH.

The electronic health records were reviewed for laboratory studies including histopathology, radiological investigations and discharge summaries to establish the cause of hypercalcemia. Treatment records and hospital course of patients diagnosed with VDT were reviewed.

Hypercalcemia was labelled if there were 2 or more readings of serum calcium (Ca) or albumin corrected calcium level above 10.2 mg/dl. Primary HPT was diagnosed if there was unequivocal hypercalcemia and high or inappropriately normal intact parathyroid hormone (iPTH) levels. VDT was diagnosed in patients with hypercalcemia and 25-hydroxy Vitamin-D (25-OHD) >150 ng/ml and low iPTH. Probable Vitamin-D toxicity (probable VDT) was labelled in patients with high Ca, suppressed iPTH and 25-OHD level between 80–149 ng/ml and no other cause of hypercalcemia. The diagnosis of multiple myeloma was based on immunofixation or bone marrow aspiration studies. The diagnoses of tuberculosis, sarcoidosis and lymphoma were made on review of histopathology, microbiology and radiological studies. The aetiology once established was reconfirmed by a second researcher. In patients where review of medical records did not reveal any diagnosis or workup was incomplete were referred to as undiagnosed cases.

Data was collected on patient demographics, age, sex, serum Ca, serum phosphorus, serum iPTH, 25-OHD, urine creatinine, urine Ca, blood urea nitrogen, clinical notes, surgical interventions, pathology reports, and radiologic reports. Complete details were recorded on a proforma.

All analyses were conducted by using the SPSS-19.0. A descriptive analysis was done and features were presented as mean±standard deviation for quantitative variables and number (Percentage) for qualitative variables.

RESULTS

Health information system generated a list of 322 patients with hypercalcemia. Review of the records revealed that 36 patients had normal serum Ca levels and 28 patients had transient hypercalcemia which did not recur during hospital stay. Out of remaining 258 patients 113 patients had solid tumour and were excluded from further analysis.

The electronic health records of remaining 145 patients were analysed to establish the aetiology of hypercalcemia. This included 100 females (69%) and 45 males (31%), with the mean age of 64.5±13.16 and mean Ca13.16±1.88 mg/dl.

HPT was the most common cause of hypercalcemia comprising 41 (28.3 %) patients. In these patients female to male ratio was 3.5:1 with mean PTH level of 638.1±762.1 pg/ml, mean calcium level 12.8±2.2 mg/dl.

Twenty-five (17.3%) had VDT; female to male ratio in these patients was 2.1:1. The mean Ca was 13.5±1.6 mg/dl. The mean 25-OHD level in four patients was 368 ng/ml and in remaining 21 patients it was reported as >150 ng/ml. Drowsiness was the most common clinical presentation. The average hospital stay was 7 days and 2 patients died during hospitalization. The cause of death in one patient was aspiration pneumonia and Non-ST elevation myocardial infarction developed during hospital course. The other patient had prolonged hospital stay in two hospitals and had infected bedsores with resultant septic shock as the cause of death. These patients underwent extensive work up for drowsiness including magnetic resonance imaging (MRI) brain, cerebrospinal fluid analysis and electroencephalogram. The diagnosis was evident by the 3rd day of hospital stay and required multiple tests including iPTH, 25-OHD, serum protein electrophoresis, and angiotensin converting enzyme levels in some cases. History of administration of multiple injections of high doses (600,000 units) of Vitamin-D_3 was available in half of the patients. It was prescribed for osteoporosis; osteoporosis related fractures and generalized body pain. Hypercalcemia was managed with administration of intravenous normal saline, furosemide and pamidronate. Subcutaneous calcitonin and oral prednisolone was used in some cases. The hypercalcemia was corrected after 3 days of the administration of pamidronate. The dose ranged from 30 to 90 mg. One patient needed a second dose of pamidronate.

In addition, 11 (7.6 %) patients had probable VDT. Female to male ratio was 2.6:1. Mean 25-OHD level was 92.7±16.1 ng/ml and mean Ca was 12.5±1.8 mg/dl. These patients had similar clinical presentation and clinical course. One patient died in this group, who was intubated because of low conscious level secondary to hypercalcemia, had prolonged hospital stay and multiple hospital acquired infections.

Other causes of hypercalcemia included multiple myeloma 18 (12.4%) patients, tuberculosis 6 (4.1%) patients, Chronic kidney disease 6 (4.1%) cases, sarcoidosis 4 (2.7%) and lymphoma 3 (2.0%) patients. In 29 (20%) patients a cause of hypercalcemia could not be ascertained and were labelled as undiagnosed cases. These patients had a PTH independent cause of hypercalcemia. However further workup was not available to reach to a definitive diagnosis. In one patient paraphenylenediamine poisoning was the cause of hypercalcemia. The frequencies of different causes with relative gender distribution are shown in table-1.

VDT and probable VDT together comprised 36 (24.8%) of the cases and one patient with HPT had 25-OHD in toxic range. Table-2 mentions the mean values of Ca, PTH and 25-OHD in various causes of hypercalcemia.

Table-1: Frequency and gender distribution of different causes of hypercalcemia

	Male	Female	Total
	45 (31%)	100 (69%)	145
Hyperparathyroidism	9 (20)	32 (32)	41 (28.3)
Undiagnosed cases	8 (17.8)	21 (21)	29 (20)
Vitamin-D toxicity	8 (17.8)	17 (17)	25 (17.2)
Multiple myeloma	7 (15.6)	11 (11)	18 (12.4)
Probable Vitamin-D toxicity	3 (6.7)	8 (8)	11 (7.6)
Tuberculosis	4 (8.9)	2 (2)	6 (4.1)
Chronic kidney disease	3 (6.7)	3 (3)	6 (4.1)
Sarcoidosis	1 (2.2)	3 (3)	4 (2.8)
Lymphoma	2 (4.)	1 (1)	3 (2.1)
Hyperparathyroidism with Vitamin-D toxicity	0 (0)	1 (1)	1 (0.7)
Miscellaneous	0 (0)	1 (1)	1 (0.7)

Table-2: Mean values of PTH, Vitamin-D and Calcium

Total (n=145)	PTH (pg/ml)	Vitamin-D (ng/ml)	Calcium (mg/dl)
Hyperparathyroidism (n=41)	638.1±762.1	48.8±84	12.8±2.2
Vitamin-D toxicity (n=25)	8.3±8.7	184.8±129.4	13.5±1.6
Probable Vitamin-D toxicity (n=11)	12.1±7.8	92.7±16.1	12.5±1.8
Undiagnosed cases (n=29)	7.6±6.7	37.5±19.2	13.5±1.8
Multiple myeloma (n=18)	9.9±6.4	23.6±15.3	12.9±1.5
Tuberculosis (n=6)	5.8±3.8	18.7±10	12.4±1.1
Sarcoidosis (n=4)	6±6	23.2±7.8	13.8±1.7
Lymphoma (n=3)	4.7±2.3	24.8±6.1	15.7
CKD (n=6)	24.6±18.9	16.1±8.8	12.06±0.9
HPT with Vit D toxicity (n=1)	443	150	15.1
Miscellaneous (n=1)	7.24	6.16	14.9

Mean±SD are reported

DISCUSSION

HPT in our data remained as one the commonest cause of hypercalcemia.[1] Mean age and female preponderance of HPT patients in our study are similar to what reported by others.[12,13] Wermer *et al* reported the peak incidence of primary hyperparathyroidism in the seventh decade with most cases occur in women.[13] Primary HPT used to be presented as bones, stones and groans in the past. These days the diagnosis is generally biochemical with high serum calcium and elevated iPTH. Once biochemical diagnosis is established, localization of parathyroid adenoma is made by parathyroid scintigraphy and or by sonography by an experienced sinologist. Surgical removal of the parathyroid adenoma is the only curative therapy for primary HPT; however, patients above 50 years of age and mild hypercalcemia and no complications can be followed.[14]

VDT has emerged as the second commonest cause of hypercalcemia in our study. In 25 patients hypercalcemia can solely be attributed to vitamin toxicity. The Vitamin-D was administered in the setting of osteoporosis, related fractures and for generalized weakness. The amount of Vitamin-D taken was documented in half of the patients. Multiple injections of high dose preparations were the main etiologic factor of VDT. The exact amount of Vitamin-D taken by these patients could not be exactly quantified because of the retrospective nature of the study. In most cases, it was Vitamin-D3 600,000 IU injection given weekly for 6-8 weeks.

Koul *et al* reported 10 cases of VDT over 10 years from Kashmir valley with one patient died because of concomitant sepsis and multiorgan failure.[15] These patients again had received Vitamin-D in form of multiple injections and oral sachet for back pain, radiculopathy, osteoarthritis and generalized weakness.

Considering this overenthusiastic practice of Vitamin-D replacement we recently have published a randomized control trial comparing replacement strategies with oral and intramuscular doses of commonly used preparations. Our study showed that a single dose of 600,000 units of Vitamin-D3 corrected the VDD in 94% of the participants and multiple injections were not required to correct the VDD.[5]

The upper limit of 25-OHD levels has not been defined. Studies in lifeguards, farmers near the equator, and sun dwelling hunter gatherers shown that they maintain blood levels between 40–80 ng/ml on sun exposure alone.[16] Marcus *et al* has reported a case of hypercalcemia in a patient with multiple sclerosis with 25-OHD level of 103ng/ml and no other identifiable cause of hypercalcemia.[17] In our study, we have identified 11 patients with unequivocal hypercalcemia, low iPTH and 25-OHD level ranging from 80–149 pg/ml. We characterized them as probable Vitamin-D toxicity. Patients in this group exhibit significant hypercalcemia and similar hospital course as patients with VDT.

Multiple Myeloma presented as third important cause of hypercalcemia after HPT and VDT. This diagnosis is generally sought very commonly in medical units, and in our study serum protein electrophoresis was done in most patients. Other causes of hypercalcemia in our study include tuberculosis, chronic kidney disease, sarcoidosis and lymphoma.

The work up of hypercalcemia after the availability of intact PTH assays has been simplified into PTH dependent and independent causes. PTH dependent causes include Primary HPT as the commonest cause, and rarely prolonged lithium use, familial hypocalciuric hypercalcemia and tertiary hyperparathyroidism would result in similar biochemical profile. To identify a PTH independent cause remains a challenge when solid tumour malignancy is not evident. The causes of PTH independent hypercalcemia commonly include solid tumour malignancy, multiple myeloma and granulomatous diseases like tuberculosis, sarcoidosis and lymphoma.[18]

Management of acute hypercalcemia is similar irrespective of the cause; this includes aggressive hydration with intravenous normal saline, low dose furosemide once adequate fluid resuscitation is achieved, and intravenous bisphosphonate. After initial treatment, management of underlying cause is important.[19]

The workup or its documentation was insufficient in 20% of cases to reach to a conclusive diagnosis; this is because of the retrospective nature of the study and it is one of the major limitations of the study.

Another limitation of our study is that we had not reviewed the management of causes of hypercalcemia other than VDT in detail. This is because the causes are varied and requires specific treatment.

CONCLUSION

Prompt identification and treatment of VDT is very important because of associated significant morbidity and mortality, prolonged hospital and costly investigations. VDT should be kept in mind in cases of PTH independent hypercalcemia, history of Vitamin-D intake should be sought and prompt treatment with hydration and intravenous bisphosphonates should be initiated. In one patient who died because of hospital acquired infections had a prolonged hospital stay and had undergone multiple investigations including bone marrow examination and trephine to evaluate the cause of hypercalcemia.

Physician education regarding replacement of Vitamin-D is of utmost importance as inadvertent administration remains the main cause of toxicity. Physician should adhere to the Endocrine Society[20] and Institute of Medicine[21] recommendations in correcting the VDD and in maintenance doses.

AUTHORS' CONTRIBUTION

MNK, MQM, MAS & SN: Conception and design. MQM, MNK, SN: Analysis and interpretation of the data. NI, MNK, MQM, SM: Critical revision of the article for important intellectual content. MQM, NI, MNK: Final approval of the article. MQM, MNK, SN, MAS: Collection and assembly of data.

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