ORIGINAL ARTICLE

PREVALENCE OF HYPERCALCEMIA OF MALIGNANCY IN PATIENTS WITH SOLID TUMORS BY MEASURING IONIZED CALCIUM IN TERTIARY CARE HOSPITAL

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ABSTRACT

Background: Hypercalcemia is relatively common in patients with cancer, occurring in approximately 20 to 30 percent of cases. As ionized calcium is not routinely estimated in most of the clinical laboratories and calcium status of the patients is being assessed by estimation of total calcium. This may result in up to 30% cases to remain undetected for hypercalcemia. The diagnosis of hypercalcemia of malignancy if made early and managed properly, could reduce this debilitating complication and objective of this study was planned to find out the prevalence of hypercalcemia of malignancy in patient with solid tumors through measurement of ionized calcium.

Methods: 73 patients diagnosed with solid tumors were included in the study. Informed consent was obtained and a proposed Performa included demographic data, Type, size, stage of tumor, duration of disease. Ionized calcium levels were performed for detection of hypercalcemia. All the patients included in the study were adult of more than 18 years and no one was suffering from hematological malignancy or with acid base disorders.

Results: A total of 73 patients, 36 females and 37 males, with mean age of 54.47 ± 15.98 were included (range 39-90 yrs in females, 19-83 yrs in males). 16 patients were suffering from Hypercalcemia of malignancy while 57 had normal ionized calcium levels.

Conclusion: Hypercalcemia of malignancy has been detected in 21.92% cases of solid tumors in our study. Further larger studies are needed to validate our data and also it is also required to find out which type of tumor is more prone to Hypercalcemia.

KEY WORDS: Hypercalcemia of malignancy, ionized calcium, solid tumors

INTRODUCTION

Hypercalcemia is relatively common in patients with cancer, occurring in approximately 20 to 30 percent of these cases. In almost 50% of patients with hypercalcemia of malignancy death occurs within a month after developing hypercalcemia.[1]

The calcium in plasma exists in three forms. Approximately 40 percent calcium in plasma is bound to albumin, 10 percent is bound to multiple organic and inorganic anions such as sulfate, phosphate, lactate and citrate, and remaining 50 percent circulates in free ionized state (Ca ++). This free ionized calcium is physiologically active [2, 3, 4] and is important for muscle contraction, nerve conduction and blood coagulation.[5] the ionized calcium concentration in plasma is tightly regulated by parathyroid hormone and vitamin "D".[6]

The reference range of total plasma calcium concentration is very wide due to variations in the plasma albumin concentration among healthy individuals due to variation in albumin bound calcium fraction in plasma. The hydration state of individual, also effects plasma albumin concentration [7, 8] thus also effecting total plasma calcium. Thus estimation of the total plasma calcium concentration alone can sometimes be misleading, since this can erroneously be interpreted as hyper or hypo-

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calcaemia on the face of normal biologically active free ionized calcium and on the other hand high and low concentrations of free ionized calcium can erroneously present in normal reference ranges of total plasma calcium. This problem becomes more pronounced in conditions associated with altered plasma proteins for example hypoalbuminemia, multiple myeloma, cirrhosis of liver and nephrotic syndrome.[7, 8]
The measured total plasma calcium concentration can be corrected for the presence of hypo or hyperalbuminemia by various equations. The most commonly practiced equation for corrected calcium is as under: [9]

Corrected calcium (mg/dl) = 0.8 × [normal albumin (4.5 g/dl) - patient's albumin (g/dl) + patient's calcium (mg/dl)]

Malignancy causes hypercalcemia in two ways. One, when a tumor grows into the bone it causes osteolysis i.e. destruction of bony tissue and secondly, when the bone metastasis is not involved, humoral factors secreted by malignant cells can increase plasma calcium levels by causing increased bone resorption and decreased renal excretion of calcium. This hypercalcemia is also known as humoral hypercalcemia of malignancy.[10,6] these two mechanisms of hypercalcemia in malignancy may operate singly or in combination.

The hormonal factor of Malignancy-Associated Hypercalcemia (MAH) has functional and structural similarity to parathyroid hormone and is known as Parathyroid Hormone related Protein (PTHrP). It is commonly associated with hypercalcemia in renal cell carcinoma, squamous cell carcinoma, and carcinoma of bladder.[11] Immobilization also causes an increase in the loss of calcium from bone; patients with cancer who are immobilized due to weakness, are more prone to hypercalcemia.[12]

Hypercalcemia of malignancy differs from other causes of hypercalcemia as it is rapid in onset, with comparatively higher serum calcium levels, and more severe symptoms.[13] The signs and symptoms of hypercalcemia are not very specific, and the clinician should have a high index of suspicion for hypercalcemia while addressing the vague presentations in managing malignancies. If hypercalcemia remains untreated then due to progressive increase in plasma calcium levels there can be deterioration of renal function and mental status. Cardiac arrhythmias and renal failure are the cause of death in this condition.[6, 13]

As free ionized calcium is not routinely estimated in most of the clinical laboratories and calcium status of the patients is being assessed by estimation of total plasma calcium. This may result in up to 30% cases to remain undetected for hypercalcemia and end up with mortalities [14]. If the calcium status of these patients is assessed with estimation of ionized calcium, the abnormality if any could be detected early and managed accordingly thus preventing much mortality.

The objective of the study is to see the prevalence of hypercalcemia in patients diagnosed for solid tumors by estimation of free ionized calcium and comparing it with total plasma calcium estimations.

METHODS

It was an observational cross sectional study. Sample size was calculated by using the W.H.O. software for "Sample Size Calculation" edited by L. Lemeshow and S. K. Lwanga using one sample situation for estimating a proportion with specified absolute precision.

This study was conducted on patients attending Oncology unit of Dr. Ziauddin Hospital, North Nazimabad, and Karachi, Pakistan. The duration of the study was from February 2014 to July 2014.

Purposive sampling technique was used to include patients in the study. Patients were selected according to the following criteria.

Inclusion criteria:
- Patients with histological proven solid tumors.
- Adults more than 18 years of age.

Exclusion criteria;
- Patients with hematological malignancies.
- Patients of solid tumors presenting with acid base disorders.

A total of 73 patients attending oncology unit, diagnosed as solid tumors were selected for the study. Approval from ethical committee of the hospital was taken prior to study. Patients were informed about the study purpose. Questionnaire was filled. Venous blood samples were collected aseptically in serum separating gel tubes and in lithium heparin tubes. The labeled samples were transported to the Chemical Pathology laboratory. Blood sample in lithium heparin tube were analyzed on Cobas b121, Roche Blood Gas Analyzer, having the facility of Ion Selective Electrode for free ionized calcium level

estimation. Blood samples in gel tube were centrifuged for 15 minutes at 3000 rpm for serum separation and analyzed on automated chemistry analyzer, Hitachi 911 for total calcium estimation by o-cresolphthalein complex one method and albumin by bromocresol green method using Roche reagents. The quality control of these analyses was censured by two levels of commercially available internal quality control materials.

Data was organized and entered on SPSS version 14.0. Continuous variables like age, duration of disease, size of tumor, calcium levels (mg/dl) were computed for Mean and standard deviation (SD). Categorical variables like gender, hypercalcemia, and stage of tumor were expressed as percentage (%). Effect modifier like age, gender, size of tumor, duration of disease and stage of tumor were controlled through stratification.

RESULTS

A total of 73 patients were included in the study. Out of these 73 patients, 36 (49.32%) were females and 37 (50.68%) were males; their age range from 39 to 90 years in females and 19 to 83 years in males. The mean age of all patients was 54.47 ± 15.98 years; in female 56.75±13.65 years, while in male the mean age was 52.24±17.87 years. (Table1). Descriptive statistics of Total calcium, Albumin corrected calcium and ionized calcium are also shown in Table 1.

Prevalence of Hypercalcemia in both male and female was seen by three reported methods of serum calcium estimation i.e., Total calcium; albumin corrected calcium and Ionized calcium. It was observed that with total calcium hypercalcemia was not detected in any of the 73 patients; only two cases (2.74%) were labeled as hypercalcemia with the estimation of albumin corrected calcium, whereas with estimation through ionized calcium, sixteen cases (21.92%) were labeled as hypercalcemia (Table 2).

It was observed during the study that hypercalcemia was most frequent 36% in age group 31- 50 years, it was 16.6% in age group >50 years and not found in age group ≤ 30years.

It was also observed that hypercalcemia was more frequent in females 27.8% than in males 16.2%. Mean size of tumor was 5.89±2.40 cm^2; in female patients it was 6.47±2.43 cm^2 and in males it was 5.32±2.23 cm^2. It was observed that frequency of hypercalcemia increases as the size of tumor increases.

Mean duration of disease was 6.96±3.20 months; in female patients the mean duration was 7.53±3.30 months and in males the mean duration of disease was 6.41±3.11 months. It was observed that frequency of hypercalcemia also increases with the duration of disease.

It was observed that hypercalcemia was 100% with metastatic disease and no hypercalcemia was found in patients having localized tumor.

Table 1: Descriptive Statistics of Age (n=73)

	n (%)	Age (Years) Mean ± SD	Total calcium(mg/dl) Mean ± SD	Albumin corrected calcium(mg/dl) Mean ± SD	Ionized calcium (mg/dl) Mean ± SD
Female	36(49.32%)	56.75 +13.65	8.19+0.85	7.70+0.74	4.72+ 0.56
Male	37(50.68%)	52.24 +17.87	8.52+1.04	7.63+1.70	4.84+ 0.64
Total	73(100%)	54.47+ 15.98	8.36+0.96	7.66+0.72	4.76+ 0.60

Table 2: Prevalence of Hypercalcemia in Both Genders (n=73)

Gender	n	Total Calcium		Albumin Corrected Calcium		Ionized Calcium	
		Hypercalcemia n(%)	Normocalcemia n(%)	Hypercalcemia n(%)	Normocalcemia n(%)	Hypercalcemia n(%)	Normocalcemia n(%)
Female	36	0(0%)	36(100%)	0(0%)	36(100%)	10(27.8%)	26(72.2%)
Male	37	0(0%)	37(100%)	2(5.40%)	35(94.60%)	6(16.2%)	31(83.8%)
Total	73	0(0%)	73(100%)	2(2.74%)	71(92.26%)	16(21.92%)	57(78.08%)

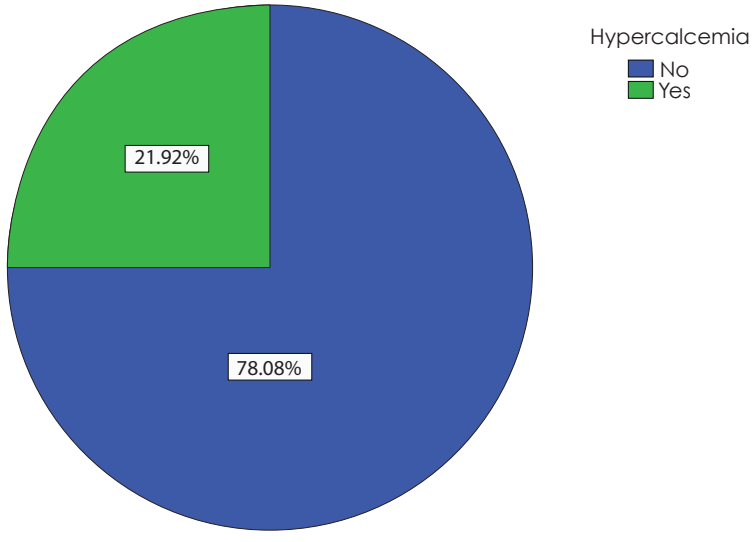

Figure 1: Precvalence of Hypercalcemia of Malignancy in patients with solid tumors by measuring ionized calcium (n=73)

DISCUSSION

Hypercalcemia is a serious and frequent complication of malignancy. It is one of the most serious metabolic disorders associated with cancer.

Almost 20 to 30 percent of patients suffering from various malignancies are also suffering from hypercalcemia and the recommended method of estimation is ionized calcium1. In the present study the hypercalcemia was present in 21.92% through estimation through ionized calcium. Ijaz A.[14], et al. concluded in his study conducted in Pakistan that ionized calcium level measurement is a better investigation for the diagnosis of hypercalcemia of malignancy as compared to total calcium estimation.

The results are similar to studies conducted in western population, but further studies are required to be conducted on much larger sample size and also it is required to find out which type of tumor is more prone to hypercalcemia. It was also noted in the study that patients with metastatic disease were having hypercalcemia and patients in which the disease were localized were having normal calcium levels which depicts that people having metastatic disease are more prone to this condition and they should be evaluated to prevent further complications. Furthermore, it was noted that patients showed hypercalcemia by measuring their ionized calcium levels; Total calcium and corrected calcium levels didn't prove to be sensitive enough to detect hypercalcemia as discussed earlier it could be because of other co-morbids associated with albumin deficiency or protein loss.

CONCLUSION

It was concluded from this study that almost 21.92% of our population who are suffering from solid tumors are also suffering from hypercalcemia of malignancy that was detected by using ionized calcium levels. These cases would not have been diagnosed as hypercalcemics it their serum calcium levels have been estimated by total calcium estimation and only 2.74% would have been detected as hypercalcemics through albumin corrected calcium estimation.

So it is emphasized that all patients suffering from malignancy should be screened for hypercalcemia by using ionized calcium levels as we have seen in this study that total calcium and corrected calcium levels are not good predictors of hypercalcemia of malignancy.

ACKNOWLEDGEMENT

The institute catered for the necessary reagents, testing kits and other expenses for this research work. Authors have no conflicts of interest that are directly relevant to the content of this manuscript.

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