Hypercalcemia in patients of oral squamous cell carcinoma

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Abstract

Purpose This study was performed to measure the total and ionic serum calcium levels and incidence of hypercalcemia in patients with Oral Squamous Cell Carcinoma (OSCC) and its clinical significance and relevance.

Materials and methods A randomly selected sample of seventy patients of histologically confirmed Oral Squamous Cell Carcinoma (OSCC) at any of the standard clinical stages were included. Fasting blood samples were obtained for measuring serum calcium levels. The elevated values of serum calcium levels were correlated with clinical features of hypercalcemia to draw inference.

Results Total serum calcium was found to be elevated in 12 patients (17.4%) and serum ionic calcium was elevated in 3 patients (4.29%).

Conclusion The data suggests that hypercalcemia occurred in advanced stages of oral squamous cell carcinoma and its management may be relevant in providing terminal care and prolonging the life span of the patients.

Keywords Hypercalcemia · Oral squamous cell carcinoma

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Introduction

Amongst the ten most common cancers in the world, oral cancer ranks eighth and its prevalence being highest in India. Hypercalcemia is one of the established complications and most common life threatening metabolic disorder associated with advanced neoplastic disease, occurring in an estimated 10%–20% of all adults and 0.5%–1% in children with cancer. The incidence of the hypercalcemia in the hematological malignancies, solid tumors like carcinoma of the breast, lung and pancreas is well documented in the literature by various authors with varied incidence. However, in the head neck malignancies the relative incidence is comparatively low as documented in the literature [1].

Hypercalcemia is caused by localized or generalized resorption of bone, releasing increased quantities of calcium into the blood. Widespread erosion of bone seen with carcinomata usually occurs because the tumor cells synthesize a substance or substances having activity like that of parathormone. Substances like osteoclast activating factor, a group of cytokines,

lymphokines, prostaglandin E, tumor growth factors, parathormone like agents, 1, 25-dihydroxy vitamin D are secreted by tumor cells which stimulate the production of cyclic adenosine monophosphate and causes increased resorption of bone, probably by reacting with receptors for parathormone [2].

Total serum calcium includes all three forms of calcium i.e., protein-bound calcium, calcium complexed with phosphate/citrate and ionized calcium. The ionic calcium exists in free form and thus it is physiologically active. Symptoms of hypercalcemia are caused by abnormalities in ionized fraction of plasma calcium concentration. The pH of blood and plasma protein concentration alters the ionized calcium fraction. Normal range of serum calcium is 9–11 mg/dl and that of serum ionic calcium is 4.7–5.2 mg/dl, which is roughly 50% of total serum calcium.

Clinical manifestations of hypercalcemia vary in severity depending on the degree and duration of hypercalcemia, rapidity of onset, age of the patient, performance status, site of metastases, previous antineoplastic therapy, and the presence of hepatic or renal

dysfunction. The clinical features of hypercalcemia are protean and affect multiple organ system resulting most prominently in neurological, gastrointestinal, renal, cardio-muscular, and musculoskeletal morbidity. Recognition of this disorder requires a high index of suspicion because many of its symptoms such as nausea, anorexia, weakness, fatigue, lethargy, and confusion are nonspecific and in the patient with malignancy can result from other complications of primary disorder. If identified appropriately as being related to hypercalcemia, such symptomatology is potentially reversible with treatment [3].

Most of the studies pertaining to finding out incidence of hypercalcemia in malignancy have been carried out in malignant tumors of breast; lung etc. and relatively fewer studies are carried out in regard to Oral Squamous Cell Carcinoma (OSCC). Hence, it was decided to find out the incidence of hypercalcemia in OSCC in Indian population where a majority of the patients report with stage III or IV disease.

As most of the patients with OSCC are cachexic and have associated findings like

anemia, the treatment planning is challenging and response to the treatment is less favorable. It was decided to evaluate whether the hypercalcemia is also present in significant number of these patients and if so, does it have any bearing on the treatment planning and its outcome.

Patients and methods

Seventy patients who had histologically proven OSCC were randomly selected in a consecutive manner for the present study. Patients without associated systemic disorders were selected irrespective of hard and soft tissue involvement by the tumour. Patients were kept fasting for 6 hours prior to obtaining the blood sample and 2 ml of blood was drawn through antecubital venepuncture using disposable syringe and 23 gauge needle. Precautions were taken not to apply tourniquet to make the veins prominent as it may induce hemolysis and interfere with the readings of ionic calcium levels in blood. The samples were collected in sterile RIA (Radio Immune Assay) tubes made up of plastic as the glass test tubes have negative charge on surface and may bind the positively charged calcium ions and interfere with subsequent readings. The serum was carefully separated using pipette which was then centrifuged to separate any residual blood cells. The serum sample was then submitted to the laboratory within 2 hours of its collection. The total serum calcium was measured using calcium estimation kit (marketed by Coral Clinical Systems, India.) This calcium kit worked on the Arsenazo III method in RA 50 chemistry auto analyzer. The serum ionic calcium was measured using Ion Selective Electrode (ISE) SnapPak® (marketed by Roche, USA) in AVL 9180 electrolyte auto analyzer. The ionic calcium and total serum calcium levels were measured and tabulated to draw an inference.

Observations and results

Out of the 70 patients, 66 (94%) of patients had stage IV lesion. Thirty patients were females and 40 were males. Forty one (58%) patients had bone involvement due to OSCC. The patients were between 28–72 years of age. The total serum calcium was elevated in 12 (17.4%) patients of which, 3 (4.29%) patients had raised serum ionic calcium levels. Of these 12 patients, 9 had involvement of bone (maxilla-3, mandible-6) and 3 patients had only soft

Table I Illustrating distribution of advance squamous cell carcinoma study patients according to site

Site of lesion	No. of patients	Percentage (%)
<i>Hard tissue</i>		
Gingivobuccal sulcus secondarily involving the maxilla	12	17
Gingivobuccal sulcus secondarily involving the mandible	29	41
<i>Soft tissue</i>		
Tongue	08	12
Buccal mucosa	14	20
Lip	03	04
Floor of mouth	02	03
Secondaries in neck with obscure primary	02	03
Total	70	100

Table II Illustrating oral squamous cell carcinoma study patients age and serum calcium values

Parameter	Age in years	Serum calcium levels	
		Total	Ionic
Mean	53	9.71	1.10
SD	11.73	1.39	0.12
SEM	1.51	0.17	0.01
95% CI	53 ± 3.02	9.71 ± 0.34	1.10 ± 0.02

· SD=Standard Deviation, SEM=Standard Error of Mean = $SD/\sqrt{n}$

· 95% Confidence Interval (CI) = Mean ± 2* SEM

tissue involvement (buccal mucosa-2, floor of mouth-1). All the patients had stage IV lesion with regional lymph node metastasis. The clinical signs of hypercalcemia like anorexia, nausea, irritability and bone pain were conspicuous in the 3 (4.29%) patients who had raised ionic calcium levels.

Discussion

Hypercalcemia in cancer patients is usually caused by advanced metastatic disease. Hypercalcemia is associated with accelerated resorption of bone which is thought to be mediated by humoral or metabolic factors [4]. Diagnostic tests like total serum calcium, serum ionic calcium, serum phosphate levels, serum magnesium levels, PTH levels, PTHrP levels are useful in the differential diagnosis of hypercalcemia and such tests together with an accurate history and careful clinical examination permit the best therapeutic approach to an individual patient. The precise diagnosis of the disorder is not only important in therapy but also to understand the various mechanisms for hypercalcemia

in cancer patients which could lead to improved modes of therapy that are more specific.

There is a distinct difference in the site predilection of oral squamous cell carcinomas in the Indian population as compared to the Western population as Western population has different tobacco habits in the form of smoked tobacco predominantly and thus, the malignancies involving the tongue, floor of mouth, pharynx are more commonly seen [5]. The tobacco habits like betel quid, pan, ghutka (smokeless tobacco) are commonly seen in the Indian population. The tobacco/quid is kept in gingivobuccal vestibule and thus, carcinoma develops at this site more often than the other parts of the oral cavity. The precipitation of the oral squamous cell carcinoma in the gingivobuccal vestibule or buccal mucosa tends to invade the underlying bone earlier and hence, it was thought that the hypercalcemia could be more commonly seen in such patients owing to erosion of the bone due to tumor invasion. A majority of the patients with oral squamous cell carcinoma report to the clinics with advanced malignancies having

significant bone involvement, extension to the cranial base and wide spread neck metastasis. At our center evaluation of such advanced tumours by thorough screening of visceral organs and long bones has not shown significant incidence of distant metastasis.

In the present study as it was observed that 12 (17.4%) patients had elevated total serum calcium and only 3 (4.29%) patients had raised ionic calcium levels. Whereas, Won C & Decker [5] found that only 2.6% of oral cancers are associated with hypercalcemia (elevated total serum calcium) and Yoneda & Nishimura [6] found it to be in 4.4% patients. Mundy & Martin and Lang-kummer [2,7] reported the incidence of hypercalcemia in 6% and 6.9% patients, respectively.

The higher incidence of hypercalcemia found in our series could be due to fact that majority of patients 66 (94%) included in study have stage IV lesion and wide spread bone involvement 41 (58%). The above finding can be collaborated with fact that hypercalcemia is known to occur in patients with advanced stages of the disease, metastatic growth and bone involvement, which is the common finding in the Indian population.

Although majority of the cases in this study had an advanced disease none of the patients had distant metastases to the viscera or long bones. The above findings may suggest that gingivobuccal malignancy with extensive bone involvement without distant metastasis is adequate to precipitate elevated serum calcium levels. The incidence of hypercalcemia is relatively more in oral squamous cell carcinoma involving bone than those tumours where only soft tissue involvement is present viz., buccal mucosa, tongue, etc. Of all the 12 (17.4%) patients with raised total serum calcium, only 1 (1.4%) had moderate (12–14 mg/dl) hypercalcemia and the remaining 11 (15.7%) had mild (10–12mg/dl) hypercalcemia [9]. Nine (12.8%) out of 12 patients of OSCC with hypercalcemia had bone involvement due to primary tumor.

The signs and symptoms of hypercalcemia like constipation, malaise-fatigue, anorexia, nausea, polyuria, lethargy and bone pain were more severe in patients

who had both raised total serum calcium and serum ionic calcium as compared to those having only raised total serum calcium. Bone pain with malignancy could be due to ischemic necrosis of bone owing to the compression of vessels by the expanding tumor mass [9] and constipation, malaise, fatigue, anorexia and nausea all of which are nonspecific findings. That they were very severe in these 3 patients and can be well correlated with the presence of hypercalcemia. All the three patients were extremely cachexic, irritable and had severe bone pain. Further enhancement of cachexia with increased dehydration leads to poor prognosis [10].

Pancreatitis, peptic ulcer disease, renal disease and renal failure can also complicate hypercalcemia. Hypercalcemia increases cardiac sensitivity to digitalis. Drugs like thiazide diuretic, lithium, antacids and vitamin D should be avoided as they are known to cause hypercalcemia. Hypercalcemia is a medical emergency and should be corrected prior to taking the patient for surgery. Ionized calcium should be closely monitored. If surgery is performed, intraoperative saline diuresis should be continued to avoid hypovolemia. Central venous or pulmonary artery pressure monitoring is advisable for patients with decreased cardiac reserve. Periodic measurements of serum potassium and magnesium are helpful in detecting iatrogenic hypokalemia and hypomagnesaemia. Responses to anesthetic agents are not predictable. Acidosis should be avoided as it can lead to elevated plasma ionic calcium levels causing further complications [11].

Conclusion

In the present study hypercalcemia was observed in 12 (17.4%) of the patients which is a significant finding. The early diagnosis of hypercalcemia may help in treatment planning and ensure better prognosis. Hypercalcemia hastens malignant cachexia and terminal complications. Hence, its relevance in providing terminal care and prolonging the life span of the patient is evident.

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