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ALTERATION OF SERUM BETA 2-MICROGLOBULIN IN ORAL CARCINOMA

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ABSTRACT

Serum β_2 –microglobulin (β_2–m) levels were measured in oral carcinoma patients and compared with normal healthy controls. It was observed that there was a significant rise in serum β_2–microglobulin in oral carcinoma patients. Progressively higher values were obtained as the cancer advanced clinically. Therefore the estimation of serum β_2–microglobulin may be useful as one of a battery of tests in the assessment of oral carcinoma patients.

KEY WORDS

Oral carcinoma; β_2 –microglobulin

INTRODUCTION

In oral carcinoma, the study of tumor markers have been limited. Several tumor markers (Ferritin, N-acetyl neuraminic acid, phosphohexose isomerase, CEA) with clinical promise need further evaluation. One such tumor marker is serum β_2 –microglobulin (β_2–m). It was first described and isolated from the urine of patients with tubular proteinurias by Berggard and Bearn in 1968 (1). β_2 –microglobulin is a low molecular weight, 11600 Dalton protein found on the surface of all cells except erythrocytes. It was also shown to occur in small quantities in normal human urine, plasma and cerebrospinal fluid (1). This protein is the light or β- chain of the human leucocyte antigen (HLA). It exists in two main forms free and non-covalently linked to the HLA antigens, forming an invariant part of the HLA molecules. The serum β_2 –microglobulin is in the free form (2). It consists of a single polypeptide chain with one intrachain disulfide bridge. It does not contain carbohydrate (1).

Increased β_2 –m levels have been reported in patients with oral cancer as well (3,4,5), but there are only limited studies on β_2 –microglobulin in oral cancer. Considering the high prevalence of oral malignancy the present study was carried out to find the correlation between serum β_2 –microglobulin in oral carcinoma at different stages in comparison with normal individuals and correlated with clinical staging.

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MATERIALS AND METHODS

Patients and controls: Serum was obtained from 30 untreated, clinically evident oral cancer patients, proved by clinical and histopathological evidence: 4 patients with oral keratosis (benign oral lesion) but no evidence of invasion: and 20 age and sex matched controls.

To avoid false positive results, care was taken to exclude subjects with renal, hepatobiliary disorders, systemic lupus erythomatosus, lymphoproliferative disorders as well as other malignancies. The subjects for the study were selected and grouped as follows.

Group I: 20 healthy individuals, 8 females and 12 males. Group II: 4 oral keratosis, 3 males and 1 female. Group III: 30 oral carcinoma patients, 17 males and 13 females. All patients were clinically staged according to TNM staging system of the International union against cancer (UICC). This group of patients were further divided into subgroups.

Group IIIA: 5 patients with stage I oral cancer. Group IIIB: 7 patients with stage II oral cancer. Group IIIC: 10 patients with stage III oral cancer. Group IIID: 8 patients with stage IV oral cancer.

β_2 –microglobulin assay:

Under aseptic precautions venous blood was drawn and serum separated. The samples were frozen at -70° C until assay. The serum was analyzed by Enzyme linked immunosorbent assay (β_2–microglobulin EIA kit, Immunotech, France). 2.4mg/L was used as the upper limit, when 97% of normal values are below this cut off value.

Statistical analysis: The data were analyzed by using statistical package for social sciences (SPSS) software. Cases and controls were tested for statistical significance with student's 't' test. Values of $p<0.05$ were considered significant.

RESULTS

The mean values of serum β_2–microglobulin in oral carcinoma patients and controls are given in table 1. In the controls (Group I) the mean β_2–microglobulin value was 1.58 ± 0.32 mg/L. In oral keratosis patients (Group II) the mean β_2 –m value was 2.00 ± 0.08mg/L. In oral cancer patients (Group III) the mean β_2 –m value was 2.69 ± 0.11mg/L (Table 1). Group IIIA consisted of 5 patients with stage I malignancy. The mean serum β_2 –m was found to be 2.06 ± 0.57 mg/L. Group IIIB consisted of 7 patients with stage II malignancy. The mean serum β_2 –m was found to be 2.53 ± 0.29 mg/L. Group IIIC consisted of 10 patients with stage III malignancy. The mean serum β_2 –m level in this group was found to be 2.69 ± 0.48mg/L. Group IIID consisted of 8 patients with stage IV malignancy and the mean value was found to be 3.22 ± 0.43 mg/L. Odds ratio 36 & 95% CI, 4.18 to 309.

The mean value of oral carcinoma patients was significantly higher than that in control group. As the stage of oral cancer advanced, the serum level of β_2 –m was increased as shown in the table 1. In this study, the serum level of 2.4mg/L was taken as the cut off value (6). Only 20 out of 30 oral cancer patients had elevated levels of serum β_2 –m and thus the sensitivity of 65.5%. The test showed an abnormal result in only 1 out of 20 of healthy controls and thus the specificity of 95.2%, positive predictive value 95%, negative predictive value of 66.6%, and efficiency of the test 78%.

DISCUSSION

The β_2 –microglobulin which is synthesized and secreted by lymphocytes as well as most other nucleated cells, is an intrinsic part of histocompatibility antigen. It has a low molecular weight and rapid turnover (1). Elevated levels of β_2 –m have been observed in a variety of patients mostly with advanced malignancy and other disease states (7,8,9). The concentration of serum β_2 –m was found to be increased in cases of various non neoplastic disorders like renal diseases (1,10), acquired immunodeficiency syndrome (11), psoriasis (12), non-Hodgkin's lymphoma (13), chronic myelogenous leukemias (14). Hence elevated levels of β_2 –m is not specific to oral carcinoma because it is altered in various non neoplastic and other neoplastic conditions.

In the present study the serum β_2 –m values were increased in oral cancer group, when compared with controls, and this is statistically significant ($p<0.05$) (Table 1). The increased levels of β_2 –m may be due to increased production or impaired excretion. However, as the patients in this present study did not have any disorder of renal function or other systemic ailments, & other malignancies, the increase in serum β_2–m appears to be a true phenomenon due to the malignant process involving oral carcinoma. The fact that β_2 –m values are elevated in the serum of subjects with oral malignancy is in agreement with reports (3,4,5).

The mechanism of increase in β_2 –m levels in malignancies is not known but various possible hypothesis for the increased serum levels have been put forward. The β_2 –m is a cell membrane constituent along with the HLA chain, so an accelerated membrane turnover or accelerated cell division could increase the shedding of β_2–m (15). The ability of the carcinoma cells to produce a higher concentration of β_2 –m than the non-neoplastic cells may be due to either active synthesis or increased cell breakdown or both (9).

As the predictive value of this estimation was found to be 95% and that of specificity of the test as 95.2%, this study confirms the results of other investigators in oral carcinoma. However as stated above it lacks specificity for oral carcinoma as an individual marker because it is elevated in other diseases also. Hence further studies are necessary to find out whether serum β_2–m would be of help in clinical diagnosis.

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Table 1 Serum beta 2-microglobulin levels in control and oral cancer patients

Group	Clinical condition	No: of patients	Serum β_2 –m (mg/L) (mean ± SD)	
I	Normal	30	1.58 ± 0.32	—
II	Oral Keratosis	4	2.00±0.08	p>0.05
IIIA	Oral cancer I	5	2.06 ± 0.57	p<0.05*
IIIB	Cancer stage II	7	2.53 ± 0.29	p<0.05*
IIIC	Cancer stage III	10	2.69 ± 0.48	p<0.05*
IIIC	Cancer stage IV	8	3.22 ± 0.43	p<0.05*

* Significant when compared with group I