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Research Article

Altered C-Reactive Protein Levels in Serum of Oral Precancer Patients in Comparison With Healthy Controls

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Abstract

Background: The role of inflammation in cancer is not well established although some organs of the body show greater risk of cancer when they are chronically inflamed. Recent advances in understanding complex tumor interactions have led to the discovery of an association between inflammation and cancer, in particular for colon and lung cancer, but only a very few have dealt with oral cancer & none with oral precancers. **Aims & Objectives**: To investigate pretreatment C-reactive protein (CRP) levels in oral precancers & evaluate their usefulness as prognostic markers. **Materials and Methods:** The study sample consisted of 25 control and 25 oral precancer patients (Leukoplakia, OSMF & Oral lichen planus) confirmed by histopathological examination. All samples were subjected to CRP analysis. **Results:** Highly significant differences in mean CRP levels were found (p=0.00) between control versus study group. **Conclusion:** Our findings demonstrate that prediagnostic concentrations of CRP are strongly associated with subsequent development of oral cancer.

Keywords: C-Reactive Protein;Precancerous Conditions;Oral Cancer;Head & Neck Neoplasms; Inflammation;Leukoplakia;Oral Lichen Planus;Oral Submucous Fibrosis.

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Introduction

As the incidence and death rate due to cancer have shown a sharp acceleration since the last two decades, more intense efforts are required to fight against this life threatening disease. Many investigators have been searching for a specific, reliable and easily identifiable biomarker, which can differentiate cancer patients from healthy individuals and also to find out patients with precancerous lesions who have high risk of developing cancer.[1,2] Acute phase proteins may have significant prognostic value in early cancer diagnostics. The role of C-reactive protein (CRP) in development and progression of human malignancy is obscure.

C-reactive protein, a member of the pentaxin protein family was first identified by Tilet & Francis (1930) in the plasma of patient with pneumonia and was named because of its ability to bind & precipitate the C-polysaccharide of pneumococcus. It is an alpha globulin with a molecular weight of 110,000 to 140,000 Daltons and is composed of five identical subunits which are noncovalently assembled as a cyclic pentamer. Liver is the site of its synthesis & normally present as trace constituent of serum of plasma at levels less than 0.3 mg/dl.[3]

Its physiological roles are numerous and varied, but mainly functions in host defense. CRP binds to specific macrophage receptors for IgG (FcγRI and FcγRIIa) a function important for opsonisation of bacteria. Moreover, it activates the early parts of the classical pathway of the complement system through binding to C1q and subsequent generation of fragments of C3 that are recognized by macrophage receptors. CRP however does not fully activate the classical pathway as it binds to the complement regulatory protein factor H. In this CRP enhances bacterial clearance without generating pro-inflammatory products. It was subsequently found that, in mammals, CRP reacts with a group of protein bound to nucleic acids. It is suggested that CRP reaction with the nuclei and membranes of damaged cells may serve to prevent autoantibody response. It was also shown that CRP reaction with nuclei of apoptotic cells contributes to the clearance of these to further decrease inflammation.[4]

The synthesis of CRP in the hepatocytes may be regulated by pro-inflammatory cytokines like interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor-necrosis factor (TNF), which have been linked with malignancies. Therefore, these pro-inflammatory cytokines

are currently the subject of intense studies as influencing factors in various types of tumors. It is increasingly recognized that in addition to tumor stage, the disease progression depends on a complex interaction between the tumor and the host's inflammatory response.[5]

However, it is still unclear whether CRP levels are elevated before the biological onset of cancer or if an elevated CRP level is also a risk factor for the development of cancer. Findings from the studies, however, have been inconsistent. Some authors have observed an association between elevated serum CRP levels in some cancers, like colorectal and lung.[5]

On the other hand, some researchers doubt that CRP can be regarded as a prognostic marker. However, raised CRP concentrations have been demonstrated to be an indicator of a poorer prognosis for squamous cell carcinoma (SCC) in patients with esophageal cancer but concerning the cancer of the oral cavity only a very few studies have dealt with this topic so far.[5] Oral squamous cell carcinoma (OSCC) accounts for nearly 50% of all newly diagnosed cancers in India. The prognosis of this cancer remains relatively unchanged for the past 30 years, despite advances in diagnosis and management. This is the first attempt to study the CRP levels with oral precancer as a useful prognostic marker.

Materials & Methods

The study samples were selected & prior consent has been taken from all the participants. Subjects with clinical diagnosis of leukoplakia, Oral submucous fibrosis (OSMF) & Oral Lichen Planus (OLP) were included in the study group. The present study was conducted on 50 subjects after approval by local ethical committee, of which 25 subjects were control & remaining 25 patients of oral precancer among which 15 Leukoplakia (Group A), 7 Oral Submucous Fibrosis (Group B) patients & 3 Oral lichen planus (Group C) confirmed by histopathological examination. Blood samples from all the participants were collected & C-reactive protein level was estimated using immunoturbidometry method. (The normal reference range considered as 0.0-0.6 mg/dl).

The statistical analyses were carried out to obtain the prevalence & comparison of CRP levels in precancer & control group by t-test. A correlation between histopathological grades of dysplasia & CRP levels was established using ANOVA (F) test by SPSS version 11.5.

Results

The mean CRP levels were analyzed & results presented in Table 1 & 2. On comparing mean CRP levels between control group (0.06 ± 0.42) & precancer group (0.71 ± 0.11) highly significant difference value (p = 0.00) was obtained. The mean CRP levels in precancerous groups A, B & C were 0.73 ± 0.13, 0.68 ± 0.10 & 0.69 ± 0.02 respectively. On comparing mean CRP levels in group A & B between different grades of dysplasia highly significant difference (p=0.00) was obtained whereas in Group C insignificant difference was obtained (p > 0.05).

Discussion

Acute phase proteins are defined as proteins whose concentration is altered at least 25% in response to inflammation[6] and include proteins of the complement, coagulation and fibrinolytic systems, antiproteases, transport proteins, inflammatory mediators and others.[7] Most acute phase proteins are synthesized primarily by the liver in response to proinflammatory cytokines including IL-1α, IL-1β, IL-6, tumor necrosis factor-α, transforming growth factor–β and interferon γ. The major acute phase proteins include C-reactive protein, serum amyloid A and fibrinogen whose concentration increases with inflammation but albumin and transferring concentration decreases with inflammation.[8]

Mean CRP Levels in Control Group	Mean CRP Levels in Study Group		t - Value	P - Value
0.06 ± 0.42	Group A	0.73 ± 0.13	26.76	0.000
	Group B	0.68 ± 0.10		
	Group C	0.69 ± 0.02		
	Total	0.71 ± 0.11		

Table 1: Comparison of CRP levels between control & study group.

Study group	No Dysplasia (P_0)	Mild Dysplasia (P_1)	Moderate Dysplasia (P_2)	Severe Dysplasia (P_3)	f- value	p-value
Group A	0.61 ± 0.30	0.67 ± 0.21	0.79 ± 0.10	0.94 ± 0.23	28.86	0.000
Group B	0.57 ± 0.02	0.68 ± 0.01	0.81 ± 0.00	-	107.76	0.000
Group C	0.71	0.68 ± 0.01	-	-	3.00	0.33

Table 2: Comparison of Mean C-RP levels with grades of dysplasia within each study group.

C-reactive protein is a type I acute phase protein, which can increase upto 1000 fold after the onset of a stimulus. Due to its opsonising abilities and its capability to activate human complement, CRP plays an important role in the innate host defense against different microorganisms, such as bacteria and fungi.[9] Its level gets raised in connective tissue diseases, cardiovascular diseases, infections, inflammatory bowel disease, lupus erythematosus, pneumococcal pneumonia, rheumatoid arthritis, rheumatic fever, Tuberculosis, last half of pregnancy and use of oral contraceptives.

Chronic inflammation has been long linked to cancer with an infectious cause as in stomach, liver and colon cancer which is common with inflammatory bowel disease. Patients with cancer of the oral cavity can be in poor nutritional condition. For esophageal cancer, a correlation has been shown between elevated serum CRP concentration and malnutrition with impaired immunity. Furthermore, smoking and alcohol abuse can also lead to chronic inflammation in the oral mucosa.[5]

Two hypotheses could be associated with increased CRP levels as a sign of chronic inflammation. First, the *Induction hypothesis postulated by* Rudolf Virchow (1863) that the cancer originated at site of chronic inflammation results in excessive cell proliferation and activation of a cascade of cellular actions, leading to induction of irreversible DNA damage. Second, the *Response hypothesis*: the immune response of the host as a consequence of tumor growth itself could be the reason for the elevation in CRP levels. An argument for the hypothesis that inflammation is associated with cancer is also derived from the reduced risk for colorectal cancer that has been associated with long-term use of aspirin and other non-steroidal anti-inflammatory drugs.[10,11]

Serum elevation of CRP has been reported to be an indicator of the unfavorable outcome in patients with some malignant tumors.[12] It has been shown that a high CRP serum level in patients with squamous cell carcinoma is associated with tumor progression and poor survival.[13] In the present study serum CRP levels in patients with oral precancerous lesions and conditions were significantly elevated as compared to control group.

Some authors have observed an association between elevated serum CRP levels in cancers like esophageal[13], colorectal[14], renal[15] and prostate.[16] In the present study mean CRP levels was found to be higher in severe grade of dysplasia (P_3) which is indicative of an impending malignancy. On comparing serum CRP levels among different histopathologic grades of dysplasia within Group A (Leukoplakia) and Group B (OSMF) found to be highly significant difference. But in Group C (OLP) no difference was seen between CRP levels & grades of dysplasia. This could be due to small number of OLP samples included in the study & also longer years to be required to turn into established cancer.

Many studies in the past have reported CRP levels with cancer & they proved the level of CRP changes as cancer progress. This is the first documentation to the best of our knowledge on changes in level of CRP as oral precancer progress towards established cancer. This was proved in our study since high rise in CRP when the precancer reached its severe grade of dysplasia.

Conclusion

CRP values can never be diagnostic on their own and can only be interpreted at the bedside, in full knowledge of all other clinical and pathological results. However, they can contribute powerfully to management, just as universal recording of the patient's temperature, an equally nonspecific

parameter, is of great clinical utility. However, CRP is a nonspecific marker of inflammation, and additional studies of specific cytokines that regulate acute-phase response are necessary to elucidate the mechanisms by which inflammation influences the risk of cancer & also future studies should recruit larger sample with various other types of oral precancers.

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