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Oral cancer is a life-threatening disease. It is the world’s eighth most common cancer in men.[1] Nowadays, the incidence of the oral cancer is high in developing countries, mainly in the Southern Central Asian region. In India, oral squamous cell carcinoma (OSCC) is the third most common cancer with an incidence rate of 52,000 annually. In developed countries such as the United States of America despite having accessibility to diagnostic and screening facility, the incidence is 13% with 30,000 newer cases every year. Most of the cases are diagnosed at an advanced stage with a poor overall survival rate of 5 years.[2]

In head and neck region, about 90% of the cancer is OSCC. The affected individuals are adults of sixth to seventh decades. Squamous cell carcinoma is defined as “a malignant epithelial neoplasm exhibiting squamous differentiation as characterized by the formation of keratin and/or the presence of intercellular bridges.”[3-5]

Oral cancer refers to cancer occurring in mouth and pharynx including cancers of lips, tongue, floor of the mouth, palate, gingiva, alveolar mucosa, tonsils, uvula, or salivary glands. Oral cancer (OSCC) to a larger extent is a self-induced disease as it is a multifactorial disease; understanding the factors will provide the knowledge of preventing and planning the treatment for better prognosis. In the postantibiotic era, oral cancer remains the disease of higher mortality in countries where the use of tobacco habits, in the form of chewing and/or smoking, with or without alcohol intake, has the greater risk of developing oral cancer; globally, it is recognized as the sixth most common cancer in this region. Recent studies show that the younger adults are affected more by OSCC.[6-9]

The genetic DNA level of mutation causes the alteration in the amino acid and protein produced by the cells. Several
mutations are necessary for the malignant change which leads to an increased cell proliferation in potentially malignant disorders, and when the cell escapes growth control, it becomes autonomous and malignant. The characteristic feature of basement break is seen in malignant lesion with a distant metastasis through the lymphatic and blood to lymph nodes. The involved organ shows dysfunction and death.[10]

**Influence of the Immune Response on Malignant Disease**

**Increased incidence of malignant disease with aging**

In older age individuals, there is a decreased cell mediated immune response to various antigens like dinitrochlorobenzenes, and lectins such as phytohemagglutinin (PHA). There is an increased incidence of the malignancy in the old age individuals, which may be related to the immunosuppression. Although many factors are involved in malignancy, the increased incidence of neoplasia in primary immune deficiency cases validates the concept of immune surveillance and supports the immunodeficiency’s role in malignancy. In patients with primary immune deficiencies, the incidence of malignant disease is more than 100 times that of the general population.[9,11]

The neonatally thymectomized animals which are immune compromised spontaneously develop neoplasia caused by polyomavirus.[11-15] this observation holds a strong argument against the concept of “immunologic surveillance.” The fact that such T-cell-deficient animals are susceptible to virus-induced tumors does not indicate that T-lymphocytes are involved in the development of other types of tumor. The most common malignancies in immunodeficiency are lymphoid system. Carcinoma at various sites is with selective immunoglobulin A (IgA) deficiency, a common variable immunodeficiency.[16] Oral neoplasia is less reported in primary immunodeficiency’s patients with severe degrees of immunodeficiency succumb at an early age, but the possibility that minor immune deficiencies underlying oral neoplasia has not been fully explored.[17]

**Increased incidence of neoplasia in secondary immune deficiencies**

The recipient in organ transplantation has an increased risk of malignancy at about 80 times that of matched controls due to immunosuppression. Similar to the primary immune suppression, the neoplasia is mainly of lymphomas and leukemia. In immune compromised patient there is an increased incidence of cancer in the lip and skin which are exclusively in sun-exposed areas. A short period review of 16,290 renal transplanted patients who are immunosuppressed showed no oral malignancy. But a long-term follow-up is necessary for exempting oral cancer incidence in these patients.[18,20]

**Relationship between the Mononuclear Cell Infiltrate and Lymph Node Reactivity in Head and Neck Carcinoma and Prognosis**

In oral cancer OSCC, the dysplastic epithelial cells show infiltration of mononuclear cell in the connective tissue.[21-23] The density of the inflammatory cell infiltrate is greater with the degree of severity of the dysplasia. On correlating with the histological view, the prognosis of the disease is increased where there is a dense mononuclear cell infiltrate in relation to the tumor. Lymphocytic cytotoxicity is increased in patients with head and neck cancer where there is a strong mononuclear cell infiltrate related to the tumor. The mononuclear cell infiltrate is largely of T-lymphocytes which are cell-mediated immune response for the tumor. The reactivity of the regional lymph nodes is also related to the prognosis of the disease.[24] In oral cancer, the predominance of lymphocytes pattern in regional lymph nodes with “active” and expanded inner cortex is increased number of germinal centers.[25] The prognosis is interestingly not related to the stage and grade of tumor.

Studies on lymphocytes using the surface Ig, complement receptor, and Ig Fc receptor show cells of T-lymphocyte characteristics and capable of normal lymph proliferative and mixed lymphocyte responses. However, the nodal lymphocytes appear to be unable to mediate cytolyis of antibody-coated target cells; presumably, there are therefore changes in T-lymphocyte subpopulations.[26]

**Immunologic Defects Associated with Head and Neck Cancer**

The most obvious immunologic change associated with head and neck cancer is a depression in the cell-mediated immune responses which are not significant in other carcinomas. Although it is not clear that the immune response alteration is primary or secondary to the neoplasm, the cellular responses remain depressed after surgical treatment of the tumor in patients with head and neck cancer, but it recovers in patients with adenocarcinomas, melanomas, or sarcomas. Therefore, it is possible that the immune defect in those with head and neck cancer is a primary event. However, exogenous factors may impair cell-mediated response.[26-30]

**Immunologic Changes**

In *vivo* studies on cell-mediated immunity show the impaired immunity in head and neck cancer. In a head and neck cancer patient, 56-70% of cases showed impairment in delayed hypersensitivity to dinitrochlorobenzene (DNCB) while the control had only 5%. The immune reactivity decreases by the advancement of the tumor. Although the relation is not specific, it shows that there is a correlation in early cancer (Stage I and Stage II) but not in advanced cancer.[31]

Eilber and Morton identified a strong correlation between a positive DNCB response and a good prognosis; the OSCC
cases with anergic response of 80% had a poor prognosis of 1 yr while the DNCB reactive cases showed a better response to radiotherapy, and the regression by 75% The survival rate is of >2 years for 95% of the patients; DNCB reactivity is not an invariable predictor of treatment success. Techniques for testing DNCB reactivity need standardized methods and results compared with closely matched controls.\(^{[34,35]}\)

Delayed hypersensitivity reactions to various antigens to which the patient is likely to have been exposed previously (recall antigens) may also be impaired in patients with head and neck cancer. The skin reactivity to purified protein derivative (PPD) of tuberculin is a better predictor for short-term survival than DNCB.\(^{[36]}\)

The recall antigen tests were less number of positive antigen used which are anergic to antigens such as PPD, mumps antigen, candidal antigens, or streptokinase streptodornase. Forty-five percent of the patients with cancer of the head and neck are anergic to one or more recall antigens as compared with anergy in only 8% of the controls; in summary, the prognosis in patients with cancer of the head and neck appears best where in vivo testing reveals intact cell-mediated immune response.\(^{[37,38]}\)

**In vitro tests of cell-mediated immunity**

In OSCC patients with increased serum concentrations of IgA and IgE with normal levels of IgG, IgM and IgD. The concentration IgA and IgE are increased in the saliva of OSCC patients is not known clearly may be due to the cell mediated immunity the production of both immunoglobulins being regulated by T-lymphocyte activity.\(^{[39,40]}\)

The humoral response of the head and neck cancer shows collection of plasma cells beneath the tumor islands.\(^{[41]}\) Deposition of IgG the C3 complement component on the tumor cells indicates that an immune response has occurred although it is unclear whether the IgG is deposited as antibody directed against tumor-associated antigens or as immune (antigen-antibody) complexes.\(^{[42]}\) Circulation of immune complex was detected in 75% of cancer patients, but the antigen responsible for the immune complexes remains unidentified. There is a reduction of the Fc fragments Ig receptors in the cells in head and neck cancer cells.\(^{[43]}\)

The humoral immune responses may therefore enhance tumor formation by the production of blocking factors in the serum antibody or the tumor-associated antigen and affect immune-mediated response.\(^{[44]}\) Other humoral factors of cell-mediated immune responses include several immunoreactive proteins, particularly certain serum glycoproteins such haptoglobin, α1, acid glycoproteins, and α1 antitrypsin.\(^{[45]}\)

The glycoprotein\(^{[46]}\) level in the serum is inversely related with the anergy to DNBC and defective lymphoproliferative responses to PHA; the levels of other proteins, such as prealbumin and α2 h glycoprotein\(^{[47]}\) are related directly with both the parameters. The α2 globulins in particular appear to impair the various cell-mediated immune responses both in vivo and in vitro. It is evident that humoral factors may suppress cell-mediated immune responses, and various suppressors of leukocytes may regulate cell-mediated immune responses in patients with head and neck cancer.\(^{[48]}\)

**Immunologic Changes in Relation to Possible Viral Etiology in Oral Cancer**

The serum IgA concentration increases in patients with head and neck cancer may be accounted for by specific antibody responses. There is a rise in titers of serum IgA antibodies to the herpes virus and Epstein–Barr virus (EBV) were seen in OSCC, nasopharyngeal carcinoma and not seen in other carcinoma.\(^{[49-52]}\). Nuclear-associated antigens of EBV (EBNA) found in nasopharyngeal carcinoma show antibodies to diffuse components of an early antigen of EBV.\(^{[53]}\) Titors of serum IgA antibodies (but not IgG or IgM antibodies) to HSV\(^{[54,55]}\) are increased in patients with head and neck cancer and the titer of such antibodies parallels the cell-mediated immune defect, suggesting that the virus might either cause the immune defect or be associated with it.

**Tumor-associated Antigens in Head and Neck Cancer**

Among the changes associated with neoplasia, there are changes in cellular antigens, including the reappearance of some fetal antigens. Carcinoembryonic antigen,\(^{[55]}\) an oncocytopetal antigen, is described to reappear in chemically induced oral cancer in animals and OSCC of human beings. The B2 microglobulin, a low-molecular-weight constituent of cell surface histocompatibility antigens (HLA antigens), is seen in small quantities of the serum in normal persons and in increased amounts in patients with oral cancer and premalignant lesions.\(^{[56]}\) The increased release of β2 microglobulin may reflect an immunological response to the tumor or changes in cell recognition associated with neoplasia.\(^{[57]}\)

In other tumors, the onset of malignancy is associated with the loss of some cell surface HLA antigens.\(^{[58,59]}\) The cellular antigens which may be lost in oral cancer include the blood group isoantigens A and B and receptors for the lectin Ricinus communis, indicating the changes in carbohydrate composition of the plasma membranes of the oral malignant cells.\(^{[60]}\)

**Exogenous Factors Influencing Immune Responses**

Several defined exogenous factors may decrease the immune reactivity in patients with head and neck cancer. These factors include particularly alcohol,\(^{[61]}\) especially if there is liver damage,\(^{[62]}\) malnutrition, smoking, chemotheraphy, anesthesia and surgery, and radiation therapy.\(^{[62-65]}\)

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