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Changes in peripheral blood lymphocyte phenotypes distribution in patients with oral cancer/oral leukoplakia in Taiwan

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Abstract. Oral squamous cell carcinoma (OSCC) is common in many Asian countries. The immunopathogenesis of OSCC is unclear. The authors analyzed the lymphocyte subtypes and surface activation markers in healthy Taiwanese people ($n = 130$) and patients with OSCC ($n = 97$)/oral leukoplakia (OL, $n = 28$) using flow cytometry. Univariate analysis found an elevation in the percentage of CD56+ NK cells, CD4+/CD69+ T cells, CD19+/CD69+ B cells and CD56+/CD69+ NK cells in OSCC patients relative to healthy people. The CD19+ and CD19+/CD25+ lymphocyte subtypes decreased in OSCC patients. CD56+ NK cells increased in OL patients. CD56+/CD69+ NK cells were elevated in recurrent and advanced OSCC. Multivariate analysis revealed an increase in CD56+ NK and CD19+/CD69+ cells in OL patients relative to controls. CD19+ B cells declined during progression from OL to OSCC. Betel quid chewing, alcohol, smoking, tumour location and staging showed little effect on lymphocyte subtypes. These results suggest that alterations and activation of NK cells, T and B cells are important and associated with disease status in oral carcinogenesis.

Keywords: betel quid chewing; lymphocyte phenotypes; oral leukoplakia; oral cancer; flow cytometry.

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Oral cancer is the fourth highest cause of death for men in Taiwan[14]. More than 90% of oral cancer patients chew betel quid (BQ) and some also smoke cigarettes and consume alcohol concomitantly. Individuals who have BQ chewing, smoking and drinking habits have a higher risk of oral leukoplakia (OL) and oral submucous fibrosis (OSF)[26]. This is because chemical carcinogens in the BQ, tobacco and alcohol may attack the protein, lipid and DNA of mucosal cells, leading to gene mutation, chromosomal aberrations and clinical oral cancer[30,34]. Most damaged DNA can be repaired and the transformed cells can be destroyed by the immune defense system, but some transformed cells may overcome the immune surveillance resulting in cancer development and progression[3,15,22,23,44].

Alterations of the cellular and humoral immune responses in affected tissues were

[5] These authors make an equal contribution to the first author.

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observed in patients with cancers of the breast, lung, liver and oral cavity[6]. Lymphocytes isolated from patients with potentially malignant oral disorders (PMOD) including OSF, OL and oral lichen planus (OLP) have higher division rates than those from healthy people[13]. An evident increase in the cytogenetic damage of lymphocytes isolated from patients with oral cancer is reported. Patients with oral cancer have higher leukocyte and lymphocyte counts, B lymphocyte number and circulating immune complexes than healthy people[37]. A reduction in total leukocyte and lymphocyte counts is seen in PMOD and oral cancer[33]. The above results suggest the presence of marked alterations in the immune status of patients with PMOD and cancer. Little is known about the factors that modulate the immunological changes in different stages of oral carcinogenesis.

The aim of this cross-sectional study was to explore the distribution of different subtypes of peripheral blood lymphocyte (PBL) including CD8+ cytotoxic/suppressor T cells, CD4+ helper T cells, CD19+ B cells and CD56+ natural killer (NK) cells and their activation surface markers CD25 and CD69 in healthy adult Taiwanese as assessed by flow cytometry. The detailed biologic significance of these lymphocytic phenotypes is described in Table 1. The authors analyzed whether alterations in these lymphocyte subtypes were obvious in peripheral blood mononuclear cells (PBMC) isolated from patients with oral squamous cell carcinoma (OSCC) and OL. They clarified the relationship between lymphocyte phenotypes and clinical variables in OSCC patients, to determine the influence of BQ chewing. Based on alterations in the distribution of lymphocyte phenotype in patients with OL and cancer, the authors established two models that can be used for clinical prediction of the nature and stages of oral carcinogenesis.

Materials and methods

From 2002 to 2004, 130 healthy volunteers (healthy control group), 27 patients with OL (disease control group) and 97 OSCC patients (experimental group) were included in this study after obtaining appropriate informed consent. The criteria for the healthy control group were: age 20–80 years; no history of oral cancer or PMOD; no obvious autoimmune disease; not taking any immunoactive medications at the time of enrolment; no drug abuse; no BQ chewing, smoking and drinking habits; no evident viral or bacterial infection at least 1 month prior to the study; and within normal limit for complete blood count and leukocyte classification. The OL cases included only those who had different dysplastic changes with or without OSF following histologic study. For cancer cases, only those with pathological diagnosis of squamous cell carcinoma (SCC) were chosen. Of the 130 healthy blood donors (aged 23–70 years), 80 were male (mean age 45.11 ± 13.15 years) and 50 female (mean age 44.78 ± 10.81 years). Of the 97 OSCC patients, 87 were male (mean age 54.18 ± 10.83 years), 10 were female (mean age 58.6 ± 14.51 years). All 27 patients with OL were male, with a mean age of 35.1 ± 10.83 years.

Questionnaire design

All cases of OSCC and OL were confirmed by pathology and the patients were interviewed by well-trained senior residents before enrolling in the study. For OSCC patients, a standardized, structured questionnaire was used and the clinical conditions before and after surgery (chest X ray, head and neck MRI, whole body Tc99m scintigraphy, abdominal sonography) were evaluated to obtain information on age, sex, clinical history, tumour site and TNM staging[1]. Information on oral habits was collected, such as whether the interviewee was a habitual alcohol consumer (none, occasional or social, one or more drinks per day for at least one year), a BQ chewer (none, occasional or social, one or more quids per day for at least one year) or a smoker (none, occasional or social, one or more cigarettes per day for at least one year). For BQ chewers, the duration of habit and the average daily consumption were recorded. The duration of BQ chewing was categorized as less than 10, 10–20, 20–30 and more than 30 years. The daily consumption of BQ was categorized as less than 15, 15–30 and more than 30 quids/day. Patients who were newly diagnosed with OSCC and received no prior treatment were categorized as fresh cases. Recurrent cases included those with a history of OSCC, developing a new lesion in the adjacent mucosa at least 6 months after treatment. Terminal stage oral cancer patients, who had inoperable recurrent tumour, multiple distant metastases, cachexia and died within 1 month after enrolling in the study, were regrouped into advanced cases. The pathological findings were also recorded, including cervical lymph node (LN) metastasis, tumour margin and differentiation status of SCC of the biopsy specimens.

Table 1. Monoclonal antibodies used to determine the lymphocytic phenotype and their biologic significance.

Official name[a]	Phenotype recognized	Biologic significance of this lymphocytic phenotype
CD3	Surface marker of T cell lineage	CD3 is an antigen and cluster of differentiation protein, which is a part of the T cell receptor (TCR) complex on mature T lymphocytes to generate activation signals.
CD4	Surface marker of helper/inducer T cells	CD4+ T cells may regulate B lymphocyte activity and promote the bactericidal activity of macrophages. They may also activate and stimulate the proliferation of cytotoxic T cells.
CD8	Surface marker of cytotoxic/suppressor T cells	CD8 is a transmembrane glycoprotein that can bind to a major histocompatibility complex (MHC) molecule and serve as a co-receptor for the T cell receptor (TCR) on human cytotoxic/ suppressor T cell. CD8+ T cells may destroy virally infected cells, keratinocytes and tumour cells and may influence specific patterns of immune and inflammatory responses.
CD19	Surface marker of B cells	CD19 is present on the earliest recognizable B-lineage cells during development to mature B cells, which can serve as a co-receptor for response to antigens. But the surface expression of CD19 is lost when mature to plasma cells.
CD25	Surface of late activated T, B and NK cells	CD25 is the alpha chain of the IL-2 receptor present on the surface of activated T, B and NK cells. They are expressed in activated T cells, B cells and NK cells. They can bind and respond to IL-2 to induce signals to stimulate T cell proliferation.
CD56	Surface marker of natural killer (NK) cells	NK cells express CD56 and are important in mediating innate immune response by secretion of perforin and granzyme to kill tumour cells or virus infected cells.
CD69	Surface marker of early activated T, B and NK cell	CD69 is a cell surface glycoprotein and receptor involved in lymphocyte proliferation and signalling functions in lymphocytes, natural killer (NK) cells, and platelets.

[a] Purchased from Coulter, Immunotech and Boehringer Ingelheim.

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