

Oral Squamous Cell Carcinoma Due to a Long-Term Smoking Habit: The Case Study

Silfra Yunus Kende¹, Hening Tuti Hendarti², Diah Savitri Ernawati^{2*}

1. Oral Medicine Resident, Department of Oral Medicine, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia.
2. Department of Oral Medicine, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia.

Abstract

Oral Squamous Cell Carcinoma (OSCC) is a common form of oral cancer with a multifactorial etiology, mainly associated with smoking, alcohol and individuals' genetic risk of developing oncogenes. OSCC cannot be diagnosed clinically but only by means of cytology and histopathology (HPA).

Case Presentation: A 22 year-old male attended Universitas Airlangga Hospital Dental Clinic complaining primarily of an oral ulcer on the right-hand edge of the tongue which had been growing increasingly painful since the previous week. The ulcer in question had appeared six months before, causing the patient to seek medical attention at a health centre. Despite a combination of triamcinolone acetonide and diclofenac sodium having been prescribed, the oral ulcer failed to heal. The patient acknowledged having smoked an average of 12 cigarettes a day for approximately two years before developing the condition.

Extra-oral examination confirmed the right-hand lymph nodes to be palpable, supple, and painful. Intra-oral examination revealed a major ulcer 2.5 cms in length with a necrotic base, erythema and an elevated, indurated lesion. The patient appeared to present a squamous cell carcinoma on the lateral dextra of the tongue with a differential diagnosis of chronic aphthous stomatitis.

Case management: The panoramic radiographic examination which the patient underwent confirmed no invasive presentation in the mandible bone. FNAB cytologic and direct mycologic examinations were performed revealing dysplasia cell and fungal hyphae. The patient was diagnosed with Stage III OSCC, T3N1M0 (invasive tumor, metastase in unilateral lymph nodes) and oral candidiasis before being referred to an oncology surgeon. The patient was prescribed Benzylamine HCL 0.15% as an anesthetic, analgesic oral rinse and an immune modulator drug. Moreover, he was instructed to stop smoking, use a prescribed mouthwash regularly, and increase his general oral hygiene. The final treatments administered were a hemiglossectomy and lymphadenectomy followed by a course of radiotherapy.

A long-term smoking habit represents a carcinogen initiator risk factor for gene mutation and oncogenic gene activation with delayed diagnosis and/or treatment serving to exacerbate the condition.

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Introduction

Oral Squamous Cell Carcinoma (OSCC) is one form of malignant tumor derived from

epithelial/squamous tissue.^{1,2} Approximately 95% of OSCC cases occur in individuals over 40 years old with the average age being approximately 60. The various trigger factors of carcinogenesis include; smoking, chewing tobacco and betel, alcohol, HPV Types 16 and 18 infection, exposure to sunlight, previous allogeneic hematologic stem cell transplantation (HSCT), and sideropenic anemia (Plummer-Vinson disease). Genetic factors contributing to the risk of oral cancer in smokers and alcoholics include ADH1C * 1/* 2 among whites, ADH1C *

*Corresponding author:

Prof. Diah Savitri Ernawati, DMD., M.Sc., Ph.D.,
Oral Medicine Specialist. Departement of Oral Medicine,
Faculty of Dental Medicine, Universitas Airlangga Jl.
Prof. Dr. Moestopo 47 Surabaya Indonesia.
E-mail: diah-s-e@fkg.unair.ac.id

1/* 2 or ADHA1C * 2/* 2, ALDH2*2 among Asians, while the risk-free genes oral cancer in Asians is typically the MTHFR TT genotype.^{1,2} The life expectancy of patients with OSCC is on average 5 years, a figure reduced by 35% if metastatic conditions have been detected. However, there is an estimated 5-year life expectancy of 75% in cases of early detection.⁴

The principle of OSCC therapy is to remove/resect tumors and lymphatic tissue involved (depending on several factors), with subsequent courses of radiotherapy and chemotherapy.⁵ The aim of this study is to report a case of OSCC in a 22 year-old Indonesian male patient.

Case Report

Visit 1: 1st day.

A 22 year-old male attended Universitas Airlangga Hospital Dental Clinic chiefly complaining of an oral ulcer on the right-hand edge of the tongue (Figure 1.) which had been growing increasingly painful since the week before. The ulcer in question had appeared six months previously causing the patient to seek medical attention at a health centre. Despite a combination of triamcinolone acetonide and diclofenac sodium having been prescribed, this oral ulcer failed to heal. The patient acknowledged having smoked an average of 12 cigarettes a day since approximately two years before having developed the condition.

Extra-oral examination confirmed the right-hand lymph nodes to be palpable, supple, and painful. Intra-oral examination revealed a major ulcer 2.5 cms in length with a necrotic base, erythema and an elevated, indurated lesion. The patient appeared to be presenting a squamous cell carcinoma on the lateral dextra of the tongue with a differential diagnosis of chronic aphthous stomatitis.

The panoramic radiographic examination which the patient underwent confirmed no invasive presentation in the mandible bone. FNAB cytologic and direct mycologic examinations were performed which revealed dysplasia cell and fungal hyphae. The patient was diagnosed with OSCC with stage III, T3N1M0 (invasive tumor, metastase in unilateral lymph nodes) and oral candidiasis before being referred to an oncologist surgeon. The patient was prescribed Benzydamine HCL 0.15% as an

anesthetic, analgesic oral rinse and an immune modulator drug. Moreover, he was instructed to stop smoking, use a prescribed mouthwash regularly and increase his general oral hygiene.

Control 1: 20th day.

The patient attended Universitas Airlangga hospital again to undergo FNAB cytology and direct mycology examination. Extra-oral examination revealed a right lymph node which was palpable, supple, painful and symmetrical in form. Intra-oral examination indicated the presence of white-yellow pseudomembranous plaque which could be scraped from the tongue dorsum, while mycology examination highlighted fungal hypae. The patient was prescribed nystatin drops as a topical antifungal and advised to use them regularly. Based on FNAB cytology results, the patient was diagnosed with OSCC on the tongue and referred to an oncologist surgeon (Figure 2.). A diagnosis of Stage III OSCC, T3N1M0 (invasive tumor, metastase in unilateral lymph nodes) resulted in a hemiglossectomy and lymphadenectomy followed by radiotherapy therapy being advised to the patient.

Control 2: 32nd day

The patient was unable to talk post-hemiglossectomy and lymphadenectomy, but while hospitalized during the recovery period felt his condition to be good. An extra-oral examination confirmed the patient to be using a nasogastric tube (NGT) with the regional neck lymphnode dextra resected. Intra-oral examination revealed the dorsum of the tongue to be white and painless with a NGT tube (nasogastric tube) being visible.

An HPA examination of open biopsy with hemiglossectomy result diagnosed OSCC of a well-differentiated type (Figure 3.). The patient was instructed to stop smoking, follow a soft-consistency diet, drink copious amounts of water and use oral rinse frequently.

Control 3: 4 months

The patient attended a control consultancy after the 16th. radiotherapy session and reported difficulty eating during the previous week. Following the prescribing of Lirical drugs, he was able to swallow more easily. Extra-oral examination of the area treated with radiotherapy showed multiple brown, painless macules. Intra-

oral examination showed an erythema erosion area on the oral mucosa covered by a white pseudo-membrane which was less painful. The post-radiotherapy diagnosis was one of mucositis, while a differential diagnosis was that of chemical burning.

The patient was prescribed alloclair oral rinse as a topical NSAID to reduce pain and act as a covering agent. He was instructed to stop smoking, follow a soft-consistency diet, drink plenty of water and make frequent use of oral rinse.

Discussion

Oral squamous carcinoma (OSCC) is a malignant tumor of epithelial/squamous cells whose diagnosis is confirmed by cytologic examination. Such examination will confirm the cell shape of anaplasia, metaplasia and dysplasia and the results in our patient showed darkened and enlarged cell nuclei (hyperchromatin), pleomorphism (shape variation), dipolarity (irregular cellular arrangement), atypical cell nuclei signifying high proliferation activity (mitosis) and visible thickening of epithelial tissue.⁴

The patient performed oral hygiene care by cleansing the lesion on the dorsum surface of the tongue through the application of sterile antiseptic cotton, while topical antifungal drugs in the form of nystatin drops were prescribed. The effect of nystatin is to bind ergosterols and sterols in the fungal membranes causing these to break down or inhibit ergosterol biosynthesis, thus suppressing secondary infection of candidiasis.⁶

Oral candidiasis superimposed with OSSC found on the patient's tongue was related to salivary secretion of mucus whose concentration was affected by beta-adrenergic and beta-sympathetic receptors. This was possibly due to the patient's smoking habit and use of analgesic drugs that suppress the dominant stimulus of serine secretion through the muscarinic-cholinergic receptors. One other possible factor was the presence of oncocytes cells in the salivary glands which causes the accumulation of PMN inflammatory cells in those glands.^{6,7}

The incidence of cancer is associated with age, this being the time-driven accumulation of genetic changes and the duration of exposure

to initiators and promoters which provoke chemical, physical, viral and hormonal effects in the elderly. Additional factors affecting patients include; decreased immune surveillance over time, individual organ transplantation, hematopoietic stem cell transplantation, chemotherapy treatment and HIV infection. The etiopatogenesis of OSCC involves oncogenes and tumor suppressor genes (TSGs). Activation of oncogenes, damage and loss of TSG and the genes responsible for DNA gene repair are all factors that impair cell function and division and trigger mutation resulting in the occurrence of malignant transformation. Carcinogenic groups such as tobacco can trigger hyperkeratinization by cessation. At the same time, mutations will initiate uncontrolled cell division proliferation.^{1,3}

The combined effects of tobacco and alcohol have a synergistic effect on the development of oral cancer. The dehydrative effect of alcohol on the mucosa causes increased mucosal permeability and exacerbates the potential effects of carcinogens such as tobacco which contains a range of cancer-causing substances, namely; nitrosamines, polycyclic aromatic hydrocarbons, nitrosodhanhanolamine, nitrosoproline, and polonium.

Cigarette smoke contains carbon monoxide, thiocyanate, hydrogen cyanide, highly addictive nicotine and a metabolism of these components. Epidemiological studies have reported that more than 80% of oral cancers occur in smokers. Furthermore, the risk of developing new primary cancers is due to a post-therapy resumption of smoking. It is significant that the patient in this case had a smoking habit. Among individuals observed over a one-year period, 18% developed primary oral cancers, while those who continued smoking were at a 30% risk of the cancer re-occurring.

The risk of cancer exists for at least 5-10 years after a person stops smoking.^{7,8} Polycyclic aromatic hydrocarbon and *nitrosamine 4-(methylnitrosamino) - 1- (3-pyridyl) -1-butanone* plays an important role in the occurrence of carcinogens through interaction with DNA and causes genetic changes.

Nicotine itself is not to be considered to be carcinogenic, but a mixture of carcinogens with a small amount of *polycyclic aromatic hydrocarbons* (PAHs) and *4-(methylnitrosamino) -1- (3-pyridyl) -1-butanone* (NNK) will convert nicotine into a carcinogen, tumor promoter and

co-carcinogen. Carcinogens such as NNK and PAHs require metabolic activation to produce carcinogenic effects. The metabolism of carcinogens will bind covalently to DNA, usually to guanine or adenine. Nicotine aerosol sprays contain about 95% gas, mainly nitrogen, oxygen and carbon dioxide. Cigarette smoke contains both free radicals that trigger oxidative damage in humans and more than 600 mg of nitric oxide, whose alleged complex free radicals cause further redox cycle superoxidation of molecular oxygen to initiate the formation of hydrogen peroxide and hydroxyl radicals. Nitric oxide with "tar" cigarettes cause DNA single-strand plasmid pBR322 destruction, while the levels of acrolein in cigarette smoke becomes toxic to the lung cilia.^{7,9}

Metastases of tumors in the lymph nodes occur in about 40% of OSCC patients. Clinically, the hidden metastasis is about 15% to 34%.¹⁰ This process is due to the reduced intercellular adhesion of tumor cells when the matrix and progress become malignant because of loss of E-cadherin, thereby beginning to form protein expression as where mesenchymal, vimentin and N-cadherin, which support the elongation of cells, and disruption of cell polarity. This condition is Epithelial Mesenchymal Transition (EMT) and is the initial occurrence of molecular changes by affecting the behavior of these cells.¹¹

Matrix Metalloproteinase (MMP) 2 and tissue inhibitor of metalloproteinase play a role in early cancer development. Syndecan is a family of proteoglycan heparin sulfate receptors which play a role in cell adhesion with other cells and cells with matrices. Reduced syndecan was correlated with histologic stage, tumor size and invasion.

Early oral cancer progression may be associated with the polymorphism Vascular Endothelial Growth Factor (VEGF) gene. Growth factor in connective tissue is suspected to have an invasive effect and an ability to move OSCC cell lines. OSCC spreads locally and regionally through lymphatic pathways. Type 1 collagenase, heparinase, prostaglandin E2, and interleukin-1 affect the extracellular matrix and the movement of epithelial cells to become invasive.¹¹ In the basal membrane, laminin and collagen damage occurs due to invasive action. Metastasis in the lymph node is considered to have occurred when the tumour is more than 1 cm in size, fixed and hard.^{12,13}

Conclusions

The long-term smoking habit of this patient represented a risk factor for carcinogen initiators for mutations in genes and oncogenic gene activation. OSCC is very rare in young patients, it is necessary to do clinical observation, proper handling and therapy is also equally important in the care of the patient. Late detection, handling and treatment can lead to worse conditions.

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Declaration of Interest

The authors report no conflict of interest.

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