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High-Risk Oral Lesions

Oral cancer and your patients

The average lifetime risk for the development of oral squamous cell carcinoma (OSCC) for Canadians is one in 89 (1). It is the ninth most diagnosed cancer in men (one in 66), and for women, the thirteenth (one in 137). While these numbers may appear modest when compared to other cancers, some patients with high-risk oral premalignant conditions have a 70-times increased lifetime risk of OSCC. Typically, cancers deep in the body are the most likely to be diagnosed at advanced stage. Despite their more superficial location, the majority of oral cancers are diagnosed at the latest stage, the stage with the worst prognosis (1). As clinicians who spend the majority of their workday in the oral cavity, dentists and dental specialists are best positioned for the early detection of premalignant conditions and malignant lesions.

Oral cancer causes

While the causes of oral cancer are multifactorial, both extrinsic and intrinsic factors play a role in predisposing patients to its development. Some more well-known extrinsic factors include tobacco and alcohol use. Cigarette smokers are on average at a three-times increased risk of developing oral cancer; however, this risk is dose dependent. Heavy alcohol use (more than four drinks per day) is associated with a two- to 14-fold increased risk. The use of another product called betel quid (variants/other names include paan masala or guthka), more common in Asia but also easily available in North America, chewed for its psychostimulatory effects (2), can cause the condition oral submucous fibrosis (discussed in this article).

High-risk conditions/lesions

The World Health Organization (WHO) considers the following lesions/conditions to be oral potentially malignant disorders (OPMDs).

Intraoral leukoplakias (white areas), erythroplakias (red areas) and erythroleukoplakias (red and white areas) are all OPMDs that require diagnosis and management (3). These terms are clinical descriptors only, and can resemble a number of premalignant conditions, from hyperkeratosis to epithelial dysplasia and even OSCC (3). The risk associated with malignant transformation depends on a number of factors including location, number of sites affected and clinical appearance. These features need to be assessed together with a knowledge of the patient's sex, medical status and social habits (4). Leukoplakia as a group shows an annual malignant transformation rate of one per cent; however, leukoplakia of the floor of mouth has a 40 per cent risk of developing into OSCC (Figure 1A) (5). While the risk of malignant transformation can be adjusted based on the above factors, the best predictor is histological grade, making initial biopsy paramount to management (6).

Proliferative verrucous leukoplakia (PVL) is a rare condition that is less well-characterized, but certainly understood to put patients at a much higher risk of developing OSCC. PVL is associated with multiple areas of leukoplakia (> two sites), verrucous features in one area, progression over time, and recurrence in at least one area, despite treatment (7). Patients with this condition are typically females with no other risk factors and are thought to have a 40 to 100 per cent chance of developing OSCC (8).

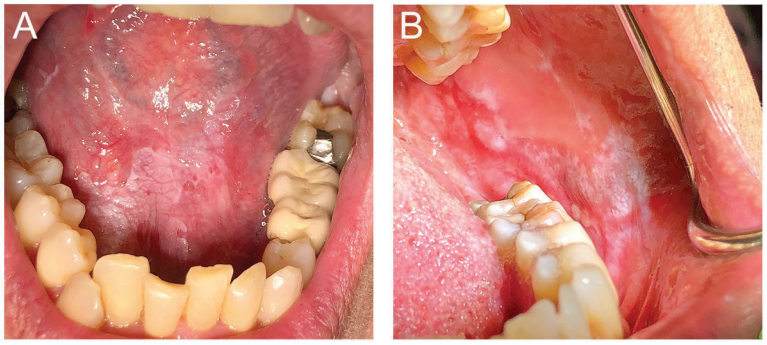

Figure 1. Clinical examples of high-risk oral lesions **A.** Epithelial dysplasia of the floor of the mouth and **B.** oral lichen planus.

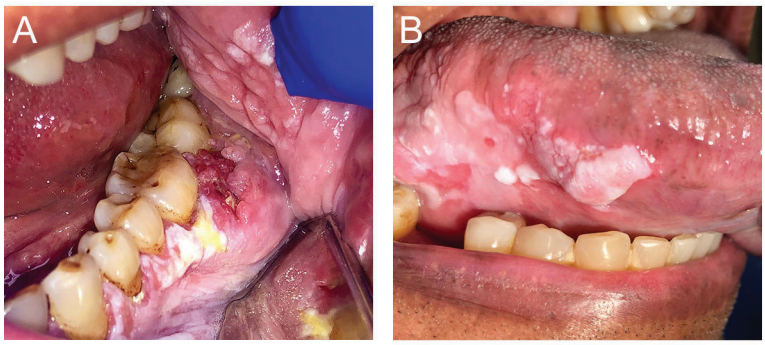

Figure 2. OSCC arising in the presence of high-risk oral lesions **A.** OSCC arising in oral submucous fibrosis and **B.** OSCC arising in oral chronic GVHD.

Oral lichen planus, another oral condition considered to be potentially malignant, is an immune-mediated condition where the skin and mucosa are attacked by the patient's own immune system. Patients with oral lichen planus are at a 0.5 to one per cent increased risk of developing oral cancer (9). This condition can present clinically with multiple red and white areas, as well as with ulcerations (Figure 1B). The most common appearance is the reticular form, where interlacing white lines (Wickham striae) can be seen, and are generally asymptomatic. The erosive form of lichen planus may appear clinically as atrophic and erythematous regions, along with ulcerations. Erosive lichen planus is generally more uncomfortable for patients. Management of this condition involves appropriate diagnosis, followed by routine examination, treatment of painful lesions, and repeat biopsy of suspicious areas as indicated.

Oral submucous fibrosis (OSF) typically comes with the complaint of trismus, which is caused by fibrosis of the oral mucosa, and a burning sensation. The patient can present with limited oral aperture due to thick fibrous banding. Intraorally, the mucosa may show pallor and stiffness of the tissues, vesicles, and lichenoid appearances with patchy white and red areas as well as ulcerations (Figure 2A). Biopsies of OSF reveal epithelial dysplasia of varying degree in 10 to 15 per cent of patients, while six per cent show OSCC (10). OSF patients have a 19-times increased risk of developing OSCC compared to the general population. Due to their high-risk nature, these patients need to be followed closely and biopsied as needed (Figure 2A shows OSCC arising in OSF). Additionally, education and cessation of betel quid is paramount.

Immunocompromised and immunosuppressive conditions can also predispose patients to the development of OSCC. This occurs due to inappropriate immunosurveillance, allowing cells with mutations to go undetected and proliferate. Additionally, a heightened immune response, leading to increased permeability of the basement membrane, may allow for invasion of dysplastic cells. This can occur in patients that have dysregulation in the immune system, either through genetic means (e.g., Fanconi anemia and Dyskeratosis congenita) or due to infections, such as human immunodeficiency virus (HIV). Immunosuppression may also occur due to immunosuppressant medications, given for a multitude of reasons: for treatment of autoimmune conditions (e.g., systemic lupus erythematosus and rheumatoid arthritis); inflammatory diseases (chronic obstructive pulmonary disease); and after transplants, be they solid organ or bone marrow/stem cell transplants. It is known that there is an increased risk in the development of OSCC in these patient populations. These patients are generally less able to withstand oncologic therapies due to medical status, and unfortunately OSCC behaviour has been shown to be more aggressive in this patient population (11).

Graft-versus-host disease (GVHD) may occur in patients who have received a stem cell or bone marrow transplant from another person to treat an underlying serious or malignant condition. The transplanted immune system may recognize the patient's skin and mucosa as foreign and attack it, resulting in a multitude of oral manifestations. Oral chronic GVHD can show features similar to lichen planus, with reticular white areas, erosions and ulcerations. It can also present as ill-defined erythema, patchy leukoplakia, vesicles, and sclerosis with accompanying xerostomia and trismus. The risk of OSCC development in these patients is 3.3 times that of the healthy population (Figure 2B) (12). The longer patients are on immunosuppressive therapy, the higher their risk of developing OSCC. Most cases of OSCC present five to nine years after transplant, but 22 per cent happen 10 years post-transplant. Therefore, the management of these patients involves lifelong follow-up.

Currently, the standard of care for monitoring precancerous lesions and conditions is with visual and tactile examination, with the adjunctive aid of tissue biopsy of any suspicious areas. With this approach of careful monitoring in these high-risk patients, the ability to detect OSCC at an early stage, which is associated with a better prognosis, is feasible. Unfortunately, while there are a number of marketed aids for the detection of OSCC, there has been no scientific evidence to confirm their ability to detect OSCC beyond conventional oral examination, and many result in false positives (13). Therefore, it is up to dentists and dental specialists to identify high-risk patients and patients with high-risk lesions within their own practice, and to ensure that they are followed closely by a clinician with a comfort level in performing biopsies, as needed for early detection and improved patient survival. OD

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