Discuss leukoplakia and erythroplakia in the oral cavity.

Abstract

Leukoplakia and erythroplakia are two common potentially malignant disorders that affect the oral cavity. The intent of this article was to present and review the current status of knowledge of oral leukoplakia and erythroplakia through a literature review. This research aims to analyse the prevalence, risk factors, clinical features, histology and the malignant potential of these lesions. Such knowledge is essential to the general dental practitioner to facilitate early detection and appropriate management of the disorders, preventing any likelihood of progression to oral cancer.

Introduction

In 2005 a World Health Organization Workshop was held to introduce a new term for oral lesions that were considered to have a predisposition for malignant transformation. The traditional term “precancerous” was scrutinized and replaced, as it wrongly implied that all such lesions would inevitably become malignant. Instead the term “potentially malignant disorders” was agreed on as instead it describes clinical presentations that carry only a risk of malignant transformation (Warnakulasuriya, Johnson & Van Der Waal, 2007).

Of such potentially malignant disorders, leukoplakia and erythroplakia are two of the most common. The purpose of understanding and identifying these lesions is centered on the ability to initiate early diagnosis and adequate intervention in lieu of malignant transformation (Kumar et al., 2013).

Research Method

Using PubMed, Cochrane Library, Embase and Medline, a search was conducted of the medical literature for articles on oral leukoplakia and erythroplakia. The key search terms used were “oral leukoplakia”, “oral precancerous lesion”, “oral erythroplakia” and “oral mucosal lesion”. Papers were considered relevant if they reported on prevalence data, classifications, risk factors, histology, clinical appearance or information regarding malignant potential. Articles included were papers published in peer review journals and in the English language. Due to the array of seminal articles that are still the foundation to much current knowledge, no strict timeframe was applied to the publishing date of the reviewed articles.

Leukoplakia

Definition

A report by Warnakulasuriya, Johnson & van der Waal (2007) acknowledged the limitations of the various definitions attributed to oral leukoplakia, and refined it to

the “term used to recognize white plaques of questionable risk having excluded any other known diseases or disorders that carry no increased risk for cancer” (p. 576).

Leukoplakia is a clinical diagnosis achieved with the atypical feature of being dependent on the exclusion of other lesions. Although leukoplakia is the common diagnosis attributed to an oral white lesion, it does not have a histological basis (Lee & Polonowita, 2009). White lesions that form the differential diagnostic list must be ruled out prior to arriving at the definitive diagnosis of leukoplakia. Such white lesions are listed in Table 1 (adapted from Warnakulasuriya, Johnson & van der Waal, 2007).

Table 1

Differential Diagnosis of Leukoplakia:

- Chemical burn
- Candidiasis: pseudomembranous, hyperplastic
- Frictional keratosis
- Hairy leukoplakia
- Leukoedema
- Linea alba
- Lichen planus
- Lichenoid reaction
- Lupus erythematosus
- Hairy leukoplakia
- Morsicatio (habitual chewing or biting of the cheek, tongue, lips)
- Papilloma and allied lesions
- Syphilis, secondary (‘‘mucous patches”)
- Smoker’s palate (nicotinic stomatitis)
- White sponge nevus

As such if an oral white lesion that was initially diagnosed as leukoplakia, can now be diagnosed as some specific condition either clinically or histologically (e.g. oral mucosal cell carcinoma), then the lesion should no longer be referred to as

leukoplakia. Specific to Candida albicans, van der Waal (2009) highlights that “there is no consensus in the literature as whether to recognize a hyperplastic subtype of oral candidiasis (as oral leukoplakia); some prefer to refer to these lesions as Candida associated leukoplakia” (p. 319).

Epidemiology

Petti (2003) inferred that the true prevalence of leukoplakia on a global scale is very likely to fall between 1.7% and 2.7%, (pp. 777-778). What resonates however is that the incidence of leukoplakia is strongly based on the population studied and their respective exposure to certain risk factors- i.e. tobacco habits (Queiroz, Medeiros, Silva & Silveira, 2014).

Gender distribution varies in most studies, however it is generally established that oral leukoplakia is more prevalent among males than females, which is attributed to males generally having an increased risk of exposure to tobacco products (Petti, 2003, Bouquot & Whitaker 1994).

A higher prevalence with increasing age is also identified with leukoplakia; often observed in men over the age of 30-40 and women over the age of 40-50. (Neville & Day, 2002, Bouquot & Whitaker 1994)

Classification

Clinical variants of leukoplakia are classified into two groups: homogeneous and non-homogenous leukoplakia.

Homogeneous leukoplakia (*Figure 1*) is defined as a lesion of uniform, flat and thin appearance, with a consistent texture throughout (Kumar et al., 2013, van der Waal, 2009).

Non- homogeneous leukoplakia is predominantly a white or mixed red-and-white lesion with an irregular texture that may be characterised appearing granular (*Figure 2*), speckled (*Figure 3*), erosive, ulcerative, or verrucous (*Figure 4*) (van der Waal 2009, Jack, Lee & Polonwinta 2009).

Proliferative verrucous leukoplakia (*Figure 5*) is a subtype of the non-homogenous verrucous leukoplakia that is not easily discernable from the more innocuous verrucous type. PVL however distinguishes itself by having variable clinical behaviour, high recurrence rate after management and a higher potential for malignancy (Cabay, Morton & Epstein, 2007).

Figure 1 Thick homogenous leukoplakia (Neville & Day, 2002)

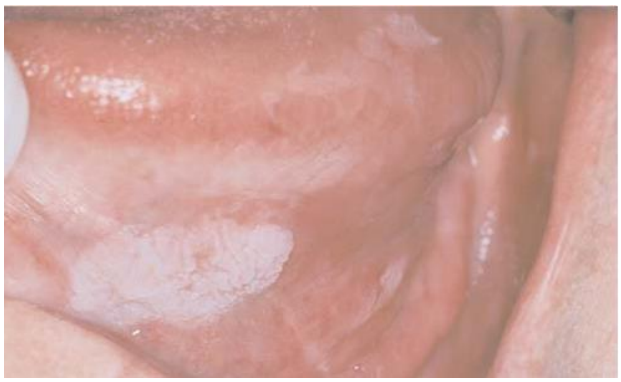


Figure 2 Granular leukoplakia (Neville & Day, 2002)

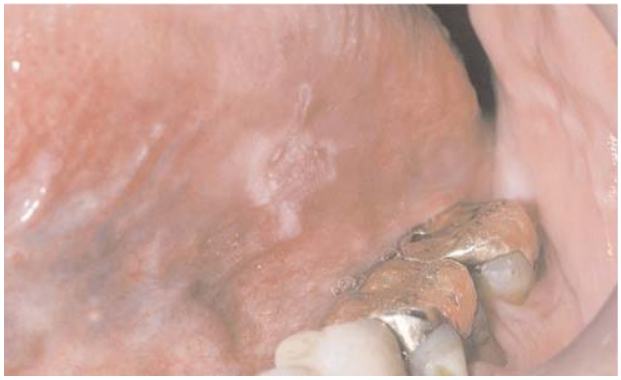


Figure 3 Speckled leukoplakia (Neville & Day, 2002)

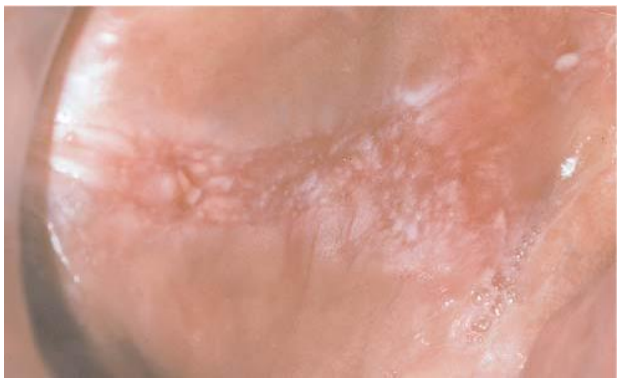


Figure 4 Verruciform leukoplakia (Neville & Day, 2002)

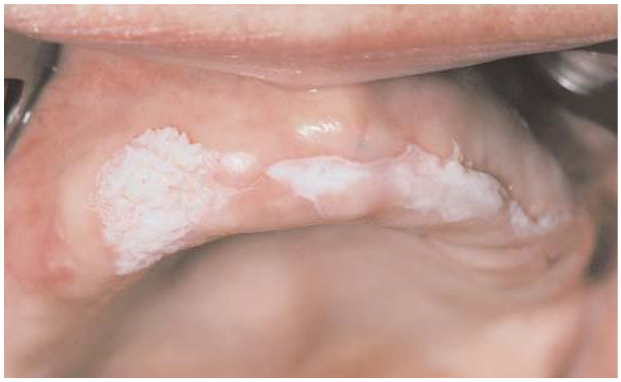
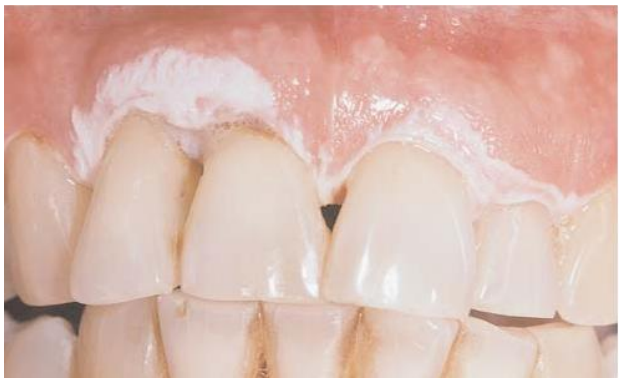


Figure 5 Proliferative verrucous leukoplakia (PVL) (Neville & Day, 2002)



Risk Factors

Tobacco

Consistent with many studies, tobacco use is the major risk factor associated with oral leukoplakia (Hashibe et al., 2000). The frequency and duration of the smoking habit is associated with an increased risk of developing the condition, thus generating a positive dose-response relationship (Dietrich, Reichart & Scheifele, 2004). Bokor-Bratic & Vuckovic (2002) found that subjects who smoked for more than 10 years, had an 11 times greater risk of developing leukoplakia than non-smokers. Concomitantly the cessation of tobacco chewing and smoking is associated with regression of the lesion, confirming its etiologic role (Banoczy, Gintner & Dombi 2001).

Alcohol

Although alcohol is a well-established risk factor for oral cancer, it is not yet a fully established risk factor for oral leukoplakia as reported findings vary (Hashibe et al., 2000). While few studies have shown a direct association of alcohol as an

independent risk factor of leukoplakia (Maserejian, Giovannucci, Rosner & Joshipura, 2006, Hashibe et al., 2000), other studies have shown no evidence with their association (Gupta, 1984, Dietrich, Reichart & Scheifele, 2004, Evstifeeva & Zaridze, 1992).

Diabetes

An association between diabetes mellitus and oral leukoplakia has been detected in research, where the incidence of leukoplakia was around 3 times more prevalent in patients diagnosed with the condition (Dietrich, Reichart & Scheifele, 2004, Albrecht, Banoczy, Dinya & Tamas, 1992).

Malignant potential

Leukoplakia is an oral lesion with a potential for malignancy and transformation to oral mucosal squamous cell carcinoma (OMSCC), thus it should be identified and managed judiciously. A form of epithelial alteration was found from 17-25% of oral leukoplakias from a range of sites, histologically demonstrating either dysplasia, carcinoma in situ or invasive carcinoma (Waldron & Shafer, 1975, Bouquot & Gorlin, 1986).

The rate of malignant transformation of oral leukoplakia varies based on the epidemiological study, with a reported range of 2.2-17.5% (Sciubba, 1995). Notably, there are particular histological and clinical risk factors that are associated with a higher potential for malignancy that are important to discuss.

Histological dysplasia

Leukoplakia with histological evidence of dysplasia is considered the most important predictor of its potential to undergo transformation to OMSCC (Reibel, 2003,

Silverman, Gorsky, Lozada, 1984, Lumerman, Freedman and Kerpel, 1995)

The study by Silverman, Gorsky, Lozada (1984), found that 36% of lesions with microscopic dysplasia developed carcinoma within an average of 7.2 years. Lumerman, Freedman and Kerpel (1995) also found 16% of patients with oral epithelial dysplasia developed OMSCC in a period of 33.6 months.

Clinical appearance of lesion

Non-homogenous leukoplakias have an increased potential for malignancy in comparison to its homogenous counterpart, highlighting the importance of the clinical detection of the lesion (Lumerman, Freedman and Kerpel, 1995, van der Waal 2009).

A four to seven-fold increased risk of malignancy has been found in the non-homogenous types (Roed-Peterson 1971, Silverman, Gorsky, Lozada, 1984, Holmstrup, Reibel, Stoltze, Vedtofte, 2006), and the erosive type in particular demonstrates a five-fold increased potential for malignant change (Bánóczy, 1977, Lind, 1987).

Furthermore, leukoplakias with a red component have the greatest likelihood for exhibiting dysplasia or carcinoma histologically (Napier & Speight 2008, Pindborg, Jolst, Renstrup & Roed-Petersen, 1968).

Additionally, the thicker the leukoplakia, the greater the chance of finding dysplastic changes. As such, a thick homogeneous leukoplaka is more likely to show dysplastic changes than a thin homogenous leukoplakia (Neville & Day, 2002).

Site

More than two thirds of all oral leukoplakias are found at three sites: lip vermilion, buccal mucosa, and gingiva (Bouquot & Whitaker, 1994). These sites however differ from those that are associated with an increased malignant potential, which include; the lateral surface of the tongue, lower lip, and floor of the mouth (Silverman, Gorsky, Lozada, 1984, Waldron & Shafer, 1975). Additionally widespread leukoplakias have a higher potential for the development of carcinoma than do the localized lesions (Saito et al., 1999)

Size

Holmstrup, Reibel, Stoltze & Vedtofte (2006) found that if the size of the leukoplakic lesion exceeded 200 mm^2 , it was around five times more likely to undergo malignant change compared to lesions less than that size.

Gender

Females with leukoplakia generally have a higher proportion of malignant transformation, even though males are more likely to develop the lesion. (Banoczy, 1977, van der Waal, 2009).

Duration

The longer the duration of the leukoplakic lesion, the increased risk for malignant transformation (van der Waal 2009), thus highlighting the importance of early detection and intervention.

Tobacco habits:

Tobacco chewing is considered a stronger risk factor for malignant transformation of

leukoplakia than tobacco smoking, and when the habits are combined the effect is synergistic (Mehta, Gupta, Pindborg, 1981, Balaram et al., 2002). As stated by Banoczy (1977) "(tobacco) smoking seems to favour the development of oral leukoplakia, but one cannot state with certainty that smoking promotes malignant transformation of oral leukoplakia" (p 73).

Additionally, it has been found that leukoplakic lesions that remain after tobacco smoking cessation, or those that appear in non-smokers, have an increased risk for malignant potential (Napier & Speight 2008, Bouquot & Whitaker 1994). An exact explanation for this phenomenon is unclear, however it has been speculated that without tobacco playing an aetiological role, the agent potentiating the leukoplakia must be more menacing (Silverman, Gorsky, Lozada, 1984).

Human Papilloma Virus

The potential role of human papilloma virus (HPV) in the etiology and/or malignant potential of leukoplakia remains unclear as results across the literature are inconsistent (Reibel, 2003, Sciubba, 1995). Miller & Johnstone (2001) however, reported that the presence of HPV, especially the "high risk types" (HPV 16 and 17), was two to three times higher in 'pre-cancerous' oral mucosa and four to five times higher in oral squamous cell carcinomas than in normal oral epithelium (p 631).

Candida

The involvement of *Candida albicans* in the etiology or progression of leukoplakic lesions remains controversial. Roed-Peterson, Renstrup & Pindborg (1970) found a higher malignant transformation rate has been reported in leukoplakias with associated chronic candida infections.

However if the lesion is caused by a *Candida* infection, then theoretically it does not comply with the accepted definition of leukoplakia. Thus the term '*Candida*-associated leukoplakia' can be used preliminarily, but if the lesion persists after treatment of the yeast infection, then it can be considered leukoplakia as a diagnosis of exclusion (Reibel, 2003).

Histopathology

Leukoplakia can present histologically as dysplastic or non-dysplastic, and the severity of the dysplasia is based on the cellular atypia and the architectural disturbance in the epithelial layer (*Table 2*) (van der Waal 2009, Jack, Lee & Polonwinta 2009). *Figure 6* demonstrates such features histologically.

Barnes, Eveson, Reichart & Sidransky (2005) in the World Health Organization classification of tumours recognizes 5 histopathological stages in potentially malignant disorders (Table 3), but it is highlighted by van der Waal (2009) that epithelial dysplasia is a spectrum and there are restrictions when attempting to precisely label the histological appearance into a specific severity (i.e. mild, moderate, severe).

Figure 6
High-magnification photomicrograph showing cellular atypia and architectural disturbance in the epithelial layer (Jack, Lee & Polonwinta 2009).

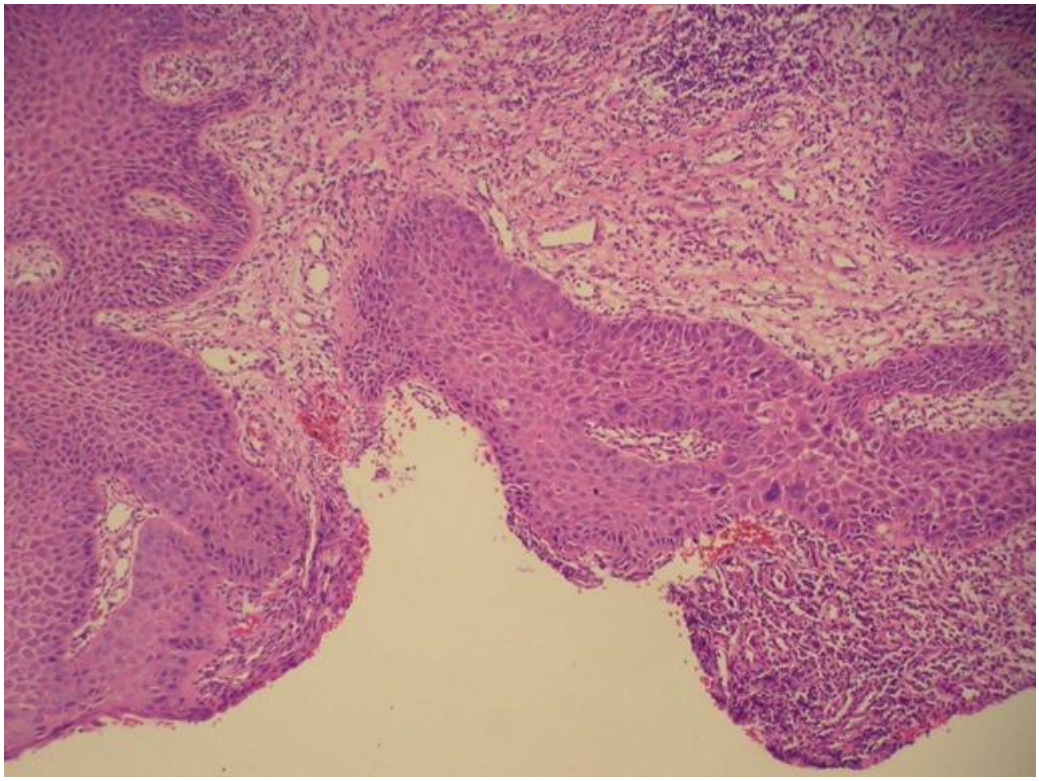


Table 2

Criteria for diagnosing dysplasia (Barnes, Eveson, Reichart & Sidransky, 2005)

<u>Architecture</u> Irregular epithelial stratification Loss of polarity of basal cells Drop-shaped rete ridges Increased number of mitotic figures Abnormal superficial mitoses Premature keratinization in single cells (dyskeratosis) Keratin pearls within rete pegs
<u>Cytology</u> Abnormal variation in nuclear size (anisonucleosis) Abnormal variation in nuclear shape (nuclear pleomorphism) Abnormal variation in cell size (anisocytosis) Abnormal variation in cell shape (cellular pleomorphism) Increased nuclear-cytoplasmic ratio Increased nuclear sizeAtypical mitotic figures Increased number and size of nucleoli Hyperchromasia

Table 3
Histopathological stages in potentially malignant disorders (Barnes, Eveson, Reichart & Sidransky, 2005)

1	Squamous hyperplasia	This may be in the spinous layer (acanthosis) and/or in the basal/parabasal cell layers (basal cell hyperplasia); the architecture shows regular stratification without cellular atypia
2	Mild dysplasia	The architectural disturbance is limited to the lower third of the epithelium accompanied by cytological atypia
3	Moderate dysplasia	The architectural disturbance extends into the middle third of the epithelium; consideration of the degree of cytological atypia may require upgrading
4	Severe dysplasia	The architectural disturbance involves more than two thirds of the epithelium; architectural disturbance into the middle third of the epithelium with sufficient cytologic atypia is upgraded from moderate to severe dysplasia
5	Carcinoma in situ	Full thickness or almost full thickness architectural disturbance in the viable cell layers accompanied by pronounced cytological atypia

Diagnosis

A provisional diagnosis of oral leukoplakia is made when possible causes of the white lesion have been eliminated, and the lesion doesn't respond to therapeutic methods within two to four weeks (van der Waal, 2010). A biopsy is then warranted to examine the specimen histologically as this will provide information on the degree of epithelial dysplasia (Jack, Lee & Polonwinta 2009). If the lesion can be given a definitive diagnosis from the histological assessment, then appropriate treatment must be sought, for example; if the lesion presents as OMSCC then referral to an oral maxillofacial surgeon is the necessary step.

Management:

There is no standard consensus on the management of leukoplakia, but if a lesion persists or shows dysplasia histologically, ablation is usually recommended (Jack, Lee & Polonwinta 2009, van der Waal, 2010). Even this however is not guaranteed to prevent reoccurance or malignant change (Vedtofte, Holmstrup, Hjørting-Hansen & Pindborg, 1987, Jack, Lee & Polonwinta 2009). Van der Waal (2009) however recommends treatment if feasible (lesions greater than 2-3mm) for all leukoplakic presentations regardless of histological dysplasia (p 320). This is particularly necessary in leukoplakic lesions that appear in high-risk sites, or in patients who have an increased risk of oral cancer due to exposure to associated risk factors e.g. tobacco users (Jack, Lee & Polonwinta 2009). A flow chart for the management of leukoplakia has been presented in Table 2.

Various non-surgical and surgical treatments have been reported, but currently there is no consensus on which treatment type best prevents recurrence or malignant transformation (Kumar et al., 2013, Jack, Lee & Polonwinta 2009). Non-surgical treatments include the use of carotenoids, vitamins A, C, and K, fenretinide, bleomycin, and photodynamic therapy have been reported, but at this time there is no evidence that this successfully prevents malignant transformation and reoccurance (Ribeiro, Salles, Da Silva & Mesquita, 2010). Invasive surgical procedures include conventional surgery, electrocoagulation, cryosurgery, and carbon dioxide laser surgery (Kumar et al., 2013, Jack, Lee & Polonwinta 2009).

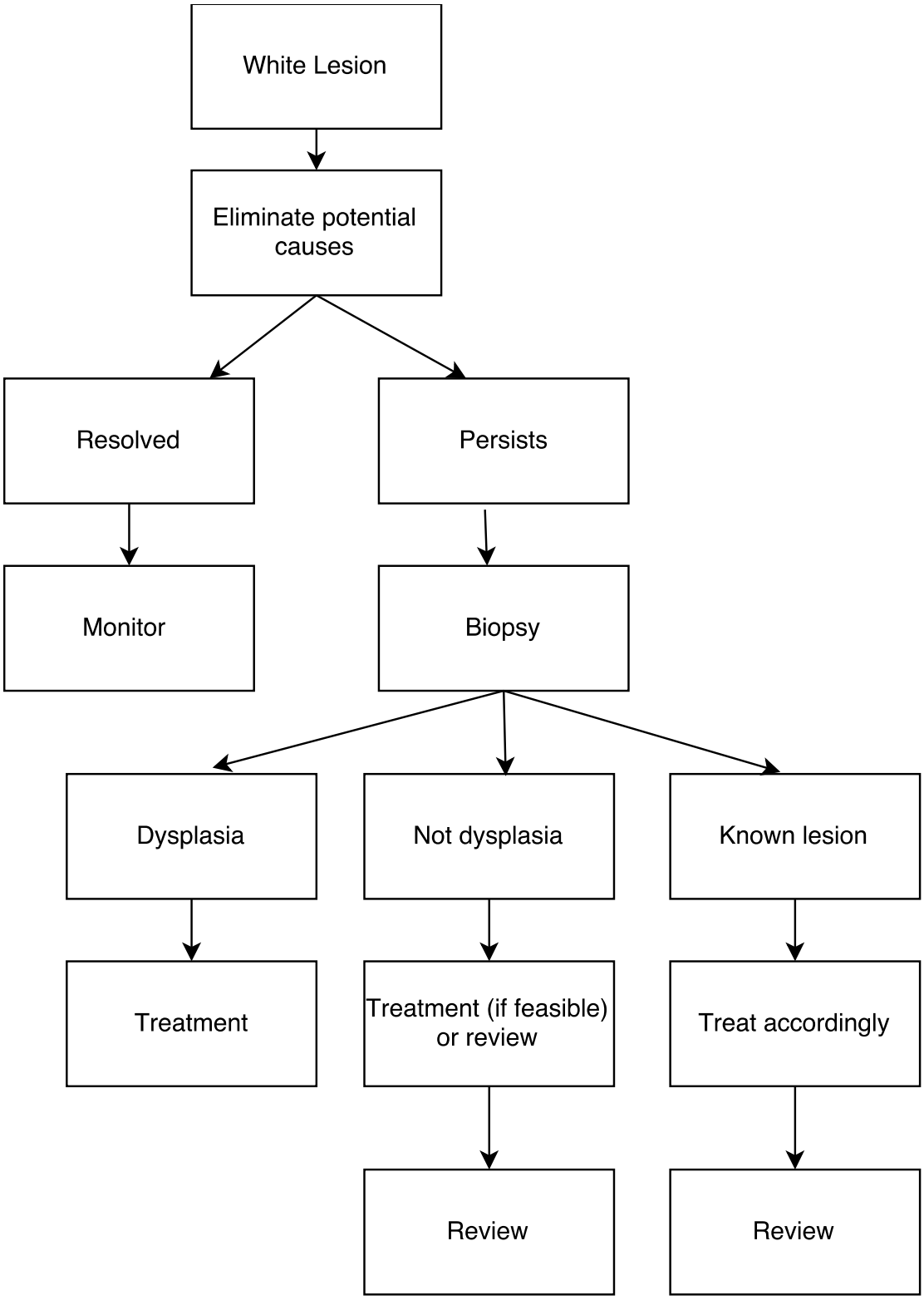
Recurrence of oral leukoplakia after surgical treatment has been reported in 10–35%

of cases (Silverman, Gorsky, Lozada, 1984, Ribeiro, Salles, Da Silva & Mesquita, 2010) and development of cancer after excision in 3–9% of cases (Holmstrup, Reibel, Stoltze, Vedtofte, 2006). Due to this, more randomised controlled trials are required to determine the effectiveness of treatment for best management (Jack, Lee & Polonwinta 2009).

The most important component in the management of leukoplakia is to maintain observation of the lesion. A six monthly review of the site and surrounding mucosa by the general dentist or specialist is essential to ensure early detection of any malignant transformation; this is advised in conjunction with well-documented clinical photographs (Jack, Lee & Polonwinta 2009).

Table 4:

Management of Leukoplakia



Erythroplakia

Definition

The definition of oral erythroplakia, consistent with 1978 WHO classification is “a fiery red patch that cannot be characterized clinically or pathologically as any other definable disease” (Warnakulasuriya, Johnson & Van Der Waal, 2007). Similar to leukoplakia, the term carries no specific histopathological connotation. (Shafer & Waldron, 1975).

Prevalence

There is a lacking aggregate of published evidence on the incidence of erythroplakia, however it is generally accepted that the prevalence of erythroplakia is much less common than it’s white lesion counterpart; oral leukoplakia.

In a study by Lapthanasupkul, Poomsawat & Punyasingh (2007), oral leukoplakia was found 13 times more frequently than erythroplakia. Reichart, Peter & Philipsen (2005) estimate that with the limited data available, the prevalence of oral erythroplakia ranges between 0.02% and 0.83%, and Villa, Villa & Abati (2011) estimate the mean prevalence of oral erythroplakia to be 0.11%.

Oral erythroplakia is also more frequently seen in patients in the later decades of their lives. Shafer & Waldron’s study (1975) observed most oral erythroplakia in the 6th and 7th decades of life. This was also the case with Lapthanasupkul, Poomsawat & Punyasingh (2007) and Hosini, Salum, Cherubini, Yurgel & Figueiredo (2009) who

found the lesion was detected between the 6th and 8th more predominantly.

There is also no notable gender predilection with oral erythroplakia (Hashibe et al., 2000, Shafer & Waldron, 1975).

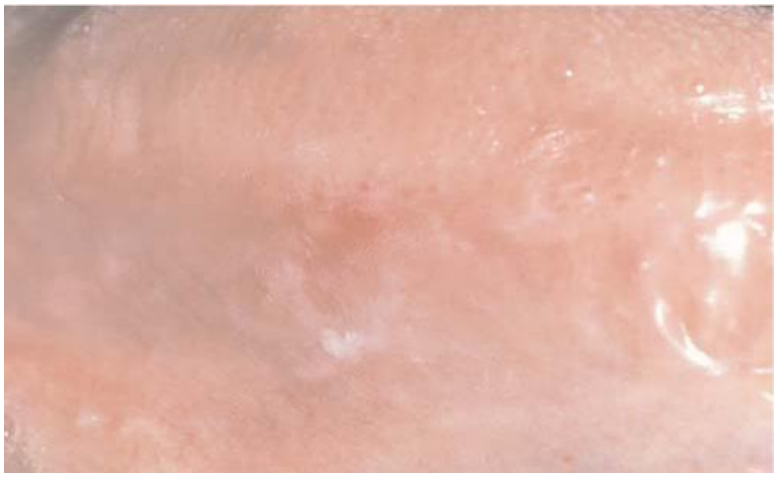
Clinical appearance

Erythroplakia can present as flat and smooth, or with a granular surface (*Figure 7*). More often however erythroplakia is seen as a mixed red-and-white lesion, referred to as either “erythroleukoplakia” or “speckled leukoplakia”. (Warnakulasuriya, Johnson, van der Waal, 2007, p. 578)

A basic problem, which has limited research in the field of erythroplakia, is in which category to include the mixed red-and-white lesions. Such lesions have been classified in the literature inconsistently under varying terms such as; “erythroplakia”, “leukoerythroplakia” and “erythroleukoplakia”. Due to this perplexity, most studies have decided to only include the homogenous type of erythroplakia in their research, restricting the data available (Reichart, Peter & Philipsen, 2005).

Villa, Villa & Abati (2011) found that erythroplakia predominately occurs on the floor of the mouth, the soft palate, the ventral tongue and the tonsillar fauces. The lesion is usually small, asymptomatic and easy to overlook, however some patients may experience a burning sensation.

Figure 7 Erythroplakia (Neville & Day, 2002)



Differential diagnosis

Similar to leukoplakia, a differential diagnosis list is essential to rule out certain conditions before arriving at the definitive diagnosis of oral erythroplakia. Such red lesions are listed in Table 3 (adapted from Reibel, 2003).

Table 5

Differential Diagnosis of Erythroplakia:

Mycotic infections

- Oral candidias:
  - Erythematous candidiasis
  - Generalized candidal erythema
  - Denture-induced stomatitis
- Histoplasmosis (oral lesion manifestation)

Bacterial infections

- Tuberculosis (oral lesion manifestation)

Mucosal diseases

- Atrophic oral lichen planus
- Lupus erythematosus
- Pemphigus vulgaris
- Mucous Membrane Pemphigoid

Others

- Amelanotic melanoma
- Haemangioma
- Telangiectasia
- Lingual varices
- Kaposi's sarcoma
- Oral purpura

Risk factors

Heavy alcohol consumption and tobacco use are known to be important risk factors for oral erythroplakia (Villa, Villa & Abati 2011).

Hashibe et al. (2000) found that tobacco chewing and alcohol drinking have a strong dose-response relationship for erythroplakia. Tobacco smoking however was a weaker risk factor. Additionally, it was found that vegetable and fruit intake are possibly protective against oral erythroplakia (Hashibe et al., 2000).
Hosni, Salum, Cherubini, Yurgel & Figueiredo (2009) highlighted in their retrospective study that all cases of erythroplakia was found in current or previous smokers, with alcohol consumption associated with 46% of cases.

Histopathology

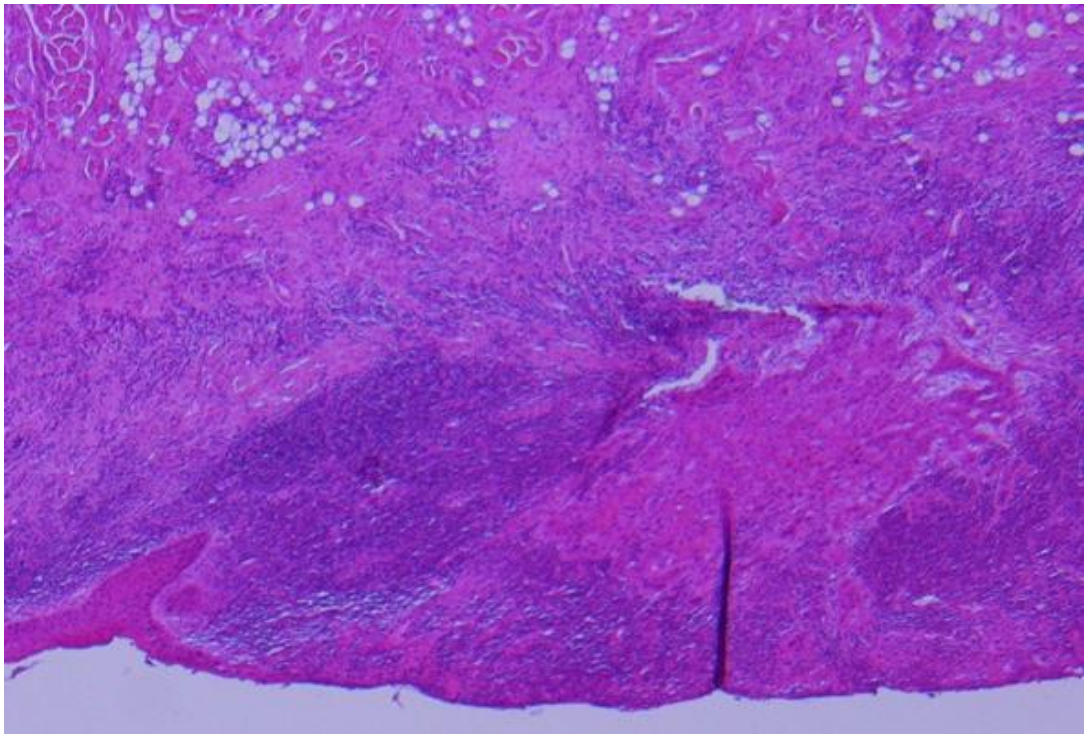
There is no clear consensus on how to clinically identify if an erythroplakic lesion will present histologically as dysplasia or carcinoma.
Shafer & Waldron (1975) studying only homogenous erythroplakia found histologically that 51% of the lesions were invasive carcinomas, 40% were carcinoma in situ or severe dysplasia, and the remaining 9% showed mild to moderate dysplasia. *Figure 8* demonstrates the histological appearance of a poorly differentiated squamous cell carcinoma.

As precise clinical markers are still lacking, this in combination with the perplexing red-and-white terminology, makes clinically assessing and grading erythroplakia challenging for clinicians (Reichart, Peter & Philipsen, 2005). In general accord

however, homogenous erythroplakic lesions or lesions with an erythroplakic component, must be treated judiciously due to the increased potential for malignant change (van der Waal, 2009)

Figure 8

High-magnification photomicrograph showing a poorly differentiated squamous cell carcinoma (Jack, Lee & Polonwinta 2009).



Malignant potential

Of all the potentially malignant disorders of the oral cavity, erythroplakia has the highest probability for malignancy (Villa, Villa & Abati 2011). Erythroplakic lesions contain areas of dysplasia, carcinoma in situ or invasive carcinoma in over 90% of cases. (Shafer & Waldron, 1975). Villa, Villa & Abati (2011) found that erythroplakia had a malignant transformation rate of approximately 44.9%.

High risks sites as ascertained by Mashberg (1977) include; floor of the mouth, ventrolateral tongue and soft palate. Notably some erythroplakic lesions can appear small and innocuous with potential to go unnoticed by clinicians, however histologically they can show carcinoma in situ (Shafer & Waldron 1975). It is for this reason, comprehensive mucosal examinations should remain an essential component to routine dental examinations.

Treatment

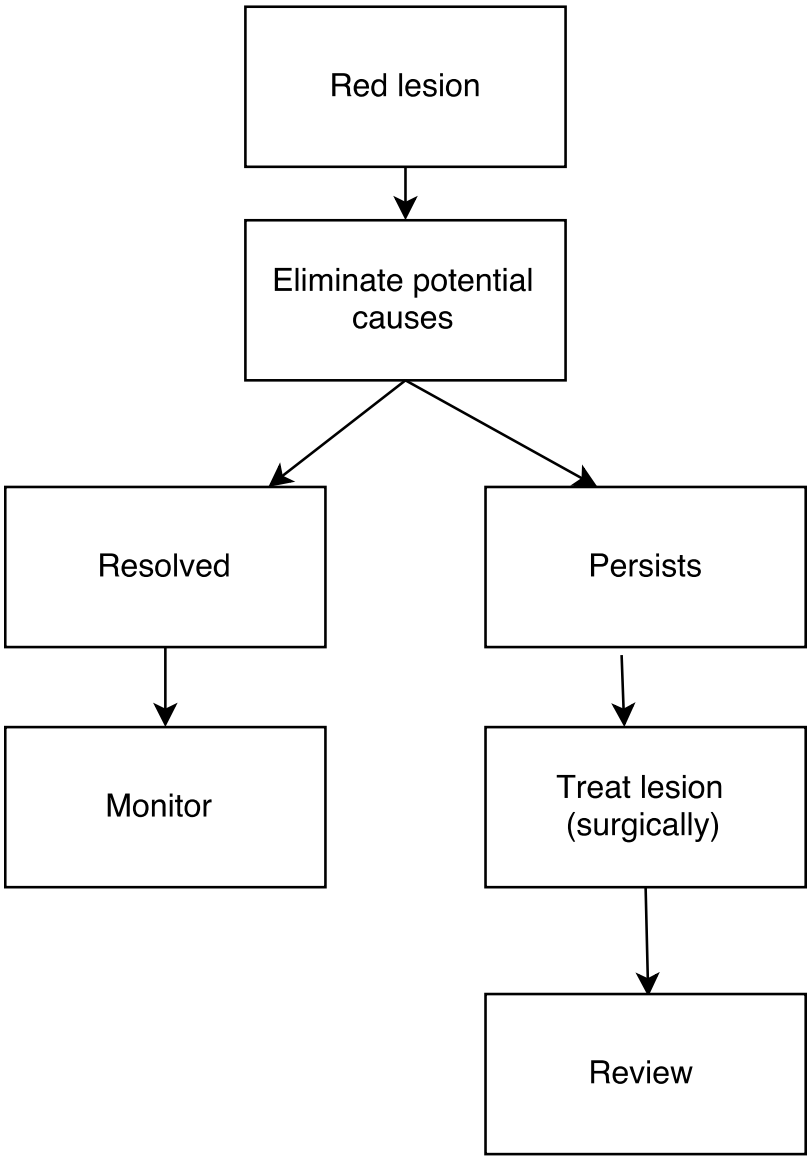
Given the known risk of erythroplakia and its malignant potential, all erythroplakias need to be treated. The recommended treatment modality is either surgery by cold knife or by laser (van der Waal 2009). The flowchart for erythroplakia thus differs to leukoplakia as treatment is undergone more proactively (see Table 3).

Irrespective of management by surgical excisions, reoccurance rates of erythroplakia are relatively high. Of the lesions studied by Vedtofte, Holmstrup, Hjørting-Hansen & Pindborg (1987), 40% of lesions with erythroplakia and 20% of lesions with erythroleukoplakia reoccurred. Amagasa, Yamashiro, & Ishikawa (2006), also recorded a recurrence of oral erythroplakia in 5 of 7 cases.

As a consequence of such findings, clinicians must ensure a disciplined protocol for recalling and monitoring patients with a history of oral erythroplakia, even after treatment has been undergone.

Table 6

Management of erythroplakia



Conclusion

Oral leukoplakia and erythroplakia are two of the most common and clinically significant mucosal lesions of the oral cavity (Warnakulasuriya, Johnson & Van Der Waal, 2007). It is well understood that with early detection of such lesions or recognizing individuals at a higher risk can prevent malignant transformation (Villa, Villa & Abati 2011).

As it is often the general dental practitioner that is the first to detect such lesions, it is essential that a sound knowledge of leukoplakia and erythroplakia be secured. This can then guide appropriate management; whether that may necessitate a biopsy or early referral.

This article thus aims to review the literature to provide such knowledge and guide clinicians to recognize and interrupt the chain of progression to oral cancer.

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