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REVIEW

Oral erythroplakia—a review

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Summary Oral erythroplakia (OE) is considered a rare potentially malignant lesion of the oral mucosa. Reports entirely devoted to OE are very few, and only two reviews none of which are of recent date have been published. Only the true, velvety, red homogeneous OE has been clearly defined while the terminology for mixed red and white lesions is complex, ill-defined and confusing. A recent case control study of OE from India reported a prevalence of 0.2%. A range of prevalences between 0.02% and 0.83% from different geographical areas has been documented. OE is predominantly seen in the middle aged and elderly. One study from India showed a female : male ratio of 1:1.04. The soft palate, the floor of the mouth and the buccal mucosa is commonly affected. A specific type of OE occurs in *chutta* smokers in India. Lesions of OE are typically less than 1.5 cm in diameter. The etiology of OE reveals a strong association with tobacco consumption and the use of alcohol. Histopathologically, it has been documented that in OE of the homogenous type, 51% showed invasive carcinoma, 40% carcinoma in situ and 9% mild or moderate dysplasia. Recently, genomic aberrations with DNA aneuploidy has been demonstrated. p53 mutations with different degrees of dysplasia may play a role in some cases of OE. Transformation rates are considered to be the highest among all precancerous oral lesions and conditions. Surgical excision is the treatment of choice. Data on laser excision are not available. Recurrence rates seem to be high, reliable data are, however, missing.

More studies on OE are strongly needed to evaluate a number of so far unanswered questions. The natural history of OE is unknown. Do OEs develop *de novo* or are they developing from oral leukoplakia through several intermediate stages of white/red lesions? The possible role of fungal infection (Candida micro-organisms) is not clear

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as is the possible role of HPV co-infection in the development of OE. More data on incidence and prevalence, biological behaviour and adequate treatment are urgently needed.

Introduction

The intent of this article was to present the current status of knowledge about oral erythroplakia (OE) through a systematic review. The following databases were searched for relevant literature using the search words: 'oral erythroplakia' and 'oral erythroplasia': MEDLINE, National Library of Medicine (PubMed) and Cochrane library. For these search words 139 items were indicated (1952—2004, PubMed). Search of the Cochrane library indicated 20 items. If the search words 'erythroplakia' and 'erythroplasia' were used 268 items were shown including literature on 'Erythroplasie de Queyrat'. If only the search word 'oral erythroplakia' was used 183 items were monitored. In addition hand searches were performed for the main oral medicine journals and books on oral mucosal diseases. Only articles in English, German and French were included in the review. Because cases of OE are often 'hidden away' in literature on oral leukoplakia (OL) and oral precancerous lesions an additional search using the term 'oral leukoplakia' was performed resulting in 2557 items (1952—2004).

Relevant papers and other texts on OE were studied for information on: historical aspects/erythroplasie de Queyrat, terminology/definition/classification, relative frequency/incidence/prevalence, clinical appearance, age, gender, location/size, geographic aspects, etiology/pathogenesis, histopathology, immunohistochemistry/ultrastructure, genomic aberrations/p53/HPV, rate of transformation, differential diagnosis, treatment and recurrence rate, and educational issues.

Generally, OE has been mentioned in a large number of reviews on oral leukoplakia but details are usually missing.[1–4] Only two rather extensive reviews on OE by Shear[5] and Shafer and Waldron[6] have been published.

Historical aspects/erythroplasia of Queyrat

In 1911 Queyrat described a sharply defined, bright red, glistening velvety precancerous lesion of the glans penis, which was termed 'erythroplasie'. Similar lesions were already described earlier by Tarnovsky (1891) and were regarded as a penile pathologic entity by Fournier in 1893.[7] Blau and Hyman,[8] in their critical evaluation of erythroplasia of Queyrat, concluded that the disease clinically involved mucosal and mucocutaneous areas of the genitalia, and that the histologic features were those of Bowen's disease of the skin. Graham and Helwig,[9] however, could show that erythroplasia of Queyrat is a distinct clinicopathologic entity different from Bowen's disease. Queyrat used the term 'erythroplasie' to designate a red area (plaque) by analogy to the French term 'leucoplasie'. Shear[5] clearly pointed out that if the English word leukoplakia is matched with 'leucoplasie', then Queyrat's 'erythroplasie' should be translated into English 'erythroplakia'. When exactly the term 'erythroplakia' was introduced to describe a specific type of oral mucosal lesion is not well documented, however, as Shear[5] stated the term at that time was only 'recently' introduced. A direct relationship between OE and the development of oral cancer was not suggested until the 1960s[10,11] and the 1970s.[12–15] Mashberg[12–15] stressed the fact that 'persistent asymptomatic erythroplakia—rather than leukoplakia—in high risk sites of the oral cavity is the earliest and primary sign of oral carcinoma'. The relative rarity of OE in comparison to oral leukoplakia has resulted in lack of a sufficient number of publications dealing with this disease entity. Also, lack of diagnostic criteria, varying definitions and classifications make comparison of individual studies difficult. Only recently the first case-control study including 100 cases of OE and 47,773 controls of an on-going randomized oral cancer screening trial in Kerala, India, has been published.[16]

Terminology/definition/classification

The term 'erythroplakia' (erythroplasia) was coined to describe red lesions of the oral mucosa in contrast to oral leukoplakia. Cawson et al.[17] drew attention to the fact that lesions of this type

(erythroplakia) do not form plaques—like oral leukoplakias—and therefore considered the term 'erythroplakia' inadequate. In contrast, these authors argued that the surface of OE is often depressed below the level of the surrounding mucosa. In addition to the term erythroplakia the term erythroleukoplakia has been introduced to describe a mixture of red and white areas of the oral mucosa. An alternative term for erythroleukoplakia has been 'erosive leukoplakia'.[18] Confusion may arise from the fact that terms like leukoerythroplakia[19] and speckled erythroplakia[20] have also been used. The latter term (speckled erythroplakia) has been suggested to replace the term speckled leukoplakia,[21] indicating the dilemma of how to quantify the amount of 'red' and 'white' areas in a given oral mucosal lesion and how to adequately name it. Some authors even only referred to 'red areas' of the palatal mucosa in *chutta* smokers (India) thus avoiding the term erythroplakia for some unknown reasons.[22]

Over the years several definitions for OE have been suggested. Mehta et al.[11] diagnosed erythroplakia ''when the oral mucosa was the seat of a well-demarcated, red, often fiery red, patch, which could not be attributed to other causes''. Shafer and Waldron[6] gave the following definition: ''Erythroplakia of the oral cavity is a specific disease entity which must be differentiated from other specific or nonspecific inflammatory oral lesions, although this can only be done in most cases by biopsy''. The WHO[23] defined OE as: ''any lesion of the oral mucosa that presents as bright red velvety plaques which cannot be characterized clinically or pathologically as any other recognizable condition''.

This definition was confirmed during an International seminar on oral leukoplakia and associated lesions related to tobacco habits in 1983.[24] In 1994,[25] at another Symposium on oral white lesions with special reference to precancerous and tobacco-related lesions the definition of OE was changed: ''The term erythroplakia is used analogously to leukoplakia to designate lesions of the oral mucosa that present as red areas and cannot be diagnosed as any other definable lesion''. As for OL the principle of provisional diagnosis and definitive diagnosis was also introduced for OE. Provisional diagnosis was defined as: ''A provisional diagnosis of OE is made when a lesion at clinical examination cannot be clearly diagnosed as any other disease of the oral mucosa with red appearance''. Definitive diagnosis was defined as: ''A definitive diagnosis of OE is made as a result of identification, and if possible elimination, of suspected aetiological factors and, in the case of persistent lesions, histopathological examination''. Bouquot and Ephros[26] proposed a further definition: ''a chronic red mucosal macule which cannot be given another specific diagnostic name and cannot be attributed to traumatic, vascular, or inflammatory causes''. In the second edition of 'Histological typing of cancer and precancer of the oral mucosa'[27] erythroplakia was defined as ''A fiery red patch that cannot be characterized clinically or pathologically as any other definable lesion''. This definition is now widely accepted, although it is based on the principle of diagnosis per exclusion.

Shear[5] suggested a classification of OE in 1972 (see Table 1). He differentiated between clinical variations and microscopic variations separating neoplastic from inflammatory changes. In this sense, OE has been classified as a neoplastic (precancerous) or inflammatory process. Later on, however, it has been suggested to use the term OE in a more restricted sense, excluding the

Table 1 Classification

(A) Clinical variations
(1) Homogeneous erythroplakia
(2) Erythroplakia interspersed with patches of leukoplakia
(3) Granular or speckled erythroplakia (embracing the lesion described as speckled leukoplakia)
(B) Microscopic variations
(1) Neoplastic
(a) Squamous carcinoma
(b) Carcinoma in situ (intra-epithelial carcinoma) and less severe forms of epithelial atypia
(2) Inflammatory
(a) Candida albicans infections (including denture stomatitis)
(b) Tuberculosis
(c) Histoplasmosis
(d) Miscellaneous specific, non-specific and non-diagnosable lesions

(Adapted from Shear.[5])

inflammation category.[28] As for OL, the term OE does not carry a histopathologic connotation.[6]

A basic problem which has been addressed by several authors[6] has been and still is in which category to include 'mixed' red and white lesions (speckled erythroplakia, leukoerythroplakia, erythroleukoplakia): (a) in the category of OE or (b) in the category of OL? Since this problem exists for all retrospective studies with inadequate documentation, some authors have decided to only include 'pure' homogeneous erythroplakia cases in their studies.[6]

Relative frequency/incidence/prevalence

It is generally accepted that OE is much less common than OL.[29] Due to its rarity case reports of OE were published until the mid 1980s.[30,31] In this context it is of interest that OE has not been included in large scale epidemiologic studies of oral mucosal lesions e.g. in an adult Swedish population,[32] in white Americans over the age of 35 years,[33] in a selected Cambodian population,[34] and a cross-sectional study of aging Germans.[35] Also, OE was not included in a 10-year follow-up study of a primary prevention trial of oral cancer in India, a study which mainly focused on stoppage of the use of tobacco and the associated decrease of the incidence rate of OL.[36]

In contrast, Mashberg and Feldman[15] drew attention to the fact that OE was seen in 64% of 236 invasive oropharyngeal carcinoma cases and in 54% of 90 cases of carcinoma in situ of the same region. Due to these findings these authors even suggested that ''it would probably be useful to eliminate the term leukoplakia from the discussion of cancer in a population of tobacco and alcohol users''(!).

Figures on relative frequency, incidence or prevalence of OE have rarely been published. Often these figures were based on retrospective analysis and on material of biopsy services.

In a survey of 50,915 Indian individuals, Mehta et al.[11] found only nine cases of OE (0.02%). In 1975 Shafer and Waldron[6] described 58 cases thought to be representative of OE among 64,345 biopsies, representing 0.09%. Two epidemiological surveys of oral mucosal lesions from Malaysia revealed a prevalence of OE of 0.02% for both studies.[37,38] In a house-to-house survey in Burma among 6000 villagers over the age of 15 years, five cases of OE were diagnosed, with a prevalence of 0.83%.[39] Feller et al.[40] from South Africa studied 138 cases of oral precancerous lesions of which eight were OEs. Bouquot and Ephros[26] reported that epidemiologic investigations of carcinoma in situ, which represents the vast majority of OEs, have found only six newly diagnosed cases per 1,000,000 persons each year. This corresponds to 1500 cases diagnosed annually throughout the United States.[26]

A recently published case-control study from Kerala, India, included 100 cases of OE among 47,773 controls, with a prevalence of 0.2%.[16] With these few data available it seems that presently OE has a range of prevalence between 0.02% and 0.83%. Of interest is that most of the prevalence figures were derived from studies in South- and Southeast-Asia; no such figures have been published from other geographic areas.

Clinical appearance

The WHO 'Histological typing of cancer and precancer of the oral mucosa'[27] described the clinical features of OE as follows: ''Some erythroplakias are smooth and some are granular or nodular. Often there is a well-defined margin adjacent to mucosa of normal appearance''. Shear[5] elaborated on the different clinical variants of OE: ''Although the erythroplakic lesions may have a smooth and velvety surface, they may also be seen with other morphological characteristics. They may have an irregular, red granular surface interspersed with white or yellow foci, which may be described as granular erythroplakia. There may be numerous, small irregular foci of leukoplakia dispersed in the erythroplakic patch, and this has been called speckled leukoplakia.[10] In fact, it is doubtful whether there is any value in distinguishing granular erythroplakia from speckled leukoplakia. Erythroplakic areas may also be found in association with or adjacent to, areas of leukoplakia''. Usually, OE is seldom multicentric and rarely covers extensive areas of the mouth. Patients in whom carcinoma in situ has been diagnosed have been aware of an alteration in the involved site for at least 2.7 years prior to biopsy.[41,42] Oral erythroplakia is soft to palpation and does not become indurated or hard until an invasive carcinoma develops in it.[26]

Oral erythroplakia, while occasionally associated with OL and oral squamous cell carcinoma, may also be observed in association with other oral mucosal diseases, in particular oral lichen planus. Holmstrup and Pindborg[43] described eight cases of OE in a cohort of 740 patients with oral lichen planus. The erythroplakic lesions in these patients

were sharply demarcated and situated at a 0.1—0.2 mm lower level than the surrounding oral mucosa. In these respects these lesions differed from the atrophic type of oral lichen planus which has no sharp demarcation and which is situated at the same level as the surrounding mucosa.

Specific palatal changes including red areas were described in *chutta* smoking, which is reverse cigar smoking (e.g. with the burning end inside the mouth) in certain areas of India.[44] These red areas and patches were characterized as well-defined reddening of the palatal mucosa and were considered to represent precancerous lesions. They were often associated with other palatal changes such as palatal keratosis (diffuse whitening of the palatal mucosa), excrescences (characterized by 1—3 mm nodules), patches (well-defined, elevated white plaques), ulcerated areas, and non-pigmented areas.[44]

Age

Oral erythroplakia mainly occurs in the middle aged and the elderly.[29] Among 58 cases of OE reported by Shafer and Waldron[6] 37 cases (67.8%) occurred in the sixth and seventh decades (19 men, 18 women), a finding confirmed by a study from South Africa.[40] Similar findings were reported from India.[45] Cases of OE ($n = 100$) were concentrated in the older age groups, compared with controls (subjects free of any oral condition or disease). The highest percentage of cases were in the 45—54-year age group (38.0%), whereas the highest percentage of controls were in the >45-year age group (39.2%).[16] It is of interest to note that patients with OE described from India are 10—20 years younger than those reported by Shafer and Waldron.[6] The median age of patients ($n = 8$) with OE and oral lichen planus was 68 years.[43]

Gender

Recently it has been stated that OE occurs mostly in men.[29] With the few studies available indicating gender distribution this statement cannot be substantiated. Shafer and Waldron[6] studied 58 case of OE and found no apparent gender predilection (27 women and 31 men; 1:1.15). In a recent study from India a gender distribution of OE ($n = 100$) of 49% in women and 51% in men (1:1.04) was reported.[16] Eight cases of OE associated with oral lichen planus all occurred in women.[43]

Location/size

The soft palate, the floor of the mouth and the buccal mucosa are most commonly affected by OE.[29] Shafer and Waldron,[6] however, observed some differences of location between women and men. The most common site of occurrence of OE in men was the floor of the mouth, but in women the combined mandibular alveolar mucosa, mandibular gingiva, and mandibular sulcus was most commonly affected. In men this combined site was the least common site of occurrence. The retromolar area in both men and women and the floor of the mouth in women was the next most common site of involvement.

The tongue is only rarely affected.[27] In patients with OE and oral lichen planus the buccal mucosa was affected in all cases ($n = 8$).[43] In *chutta* smokers of India the palate is usually affected by occurrence of red areas.[44]

The typical lesion of OE is less than 1.5 cm in diameter and half are less than 1 cm, but lesions larger than 4 cm have been observed.[26]

Geographic aspects

While OE does not seem to have a known geographic incidence,[29] studies from India have shown that OE may be associated with special smoking and chewing habits and that the risk to develop OE was strongly associated with these[16,45—47] (see below).

Etiology/pathogenesis

Etiology and pathogenesis of OE are poorly understood. Predisposing factors are widely unknown, but it was suggested that tobacco and alcohol use are probably involved in most cases.[29] A recently published series of papers based on a large case-control study in Kerala, India, shed more light on some of the factors involved in the etiology of OE.[16,45—47] One of these studies evaluated the risk of OE in relation to chewing tobacco, smoking, alcohol drinking, body mass index (BMI), and vegetable, fruit, and vitamin/iron intake. The adjusted odds ratio (OR) for OE was 19.8 (95% CI, 9.8—40.0) for individuals who had ever chewed tobacco, after controlling for age, gender, education, BMI, smoking and drinking. The adjusted OR for ever-alcohol drinkers was 3.0 (95% CI, 1.6—5.7) after controlling for age, gender, education, BMI, chewing tobacco and smoking. For forever smokers, the adjusted

OR was 1.6 (95% CI, 0.9—2.9). A more than additive interaction on the risk of OE was suggested between tobacco chewing and low vegetable intake, whereas a more than multiplicative interaction was indicated between alcohol drinking and low vegetable intake, and between drinking and low fruit intake. It was concluded that tobacco chewing and alcohol drinking are strong risk factors for OE in the Indian population. In another publication based on the same material[47] the risk of betel quid without tobacco and its relation to oral precancers including 100 cases of OE was described. Among the non-smokers and non-drinkers, chewing betel without tobacco conferred ORs of 29.0 (95% CI = 5.63, 149.5) for OE compared to 22.2 (95% CI = 11.3, 43.7) for OL and 56.2 (95% CI = 21.8, 144.8) for oral submucous fibrosis, after adjustment for age, gender, education and BMI. It was concluded that the hypothesis that chewing betel quid without tobacco elevates the risk or various precancers, including OE. The aim of another study[45] was to examine the association of education, occupation, income and socio-economic status (SES) index with oral precancers.

From this study it was concluded that, although the mechanism for an association of some of the parameters studied was not clear, higher SES index, education and income were associated with decreased risk of oral precancers, including OE. Yet another study of the same material was designed to study risk factors for multiple oral premalignant lesions.[46] The results of this study suggested that tobacco chewing was the most important risk factor for multiple oral premalignant lesions and therefore may be a major source of field cancerization on the oral epithelium in an Indian population. Reverse *chutta* smoking, as has been described in this review, is also strongly associated with the use of tobacco and heat.[44] Further of interest is that out of eight patients with OE and oral lichen planus five were smokers.[43] The possible etiology of human papillomavirus infection and OE is shortly discussed under to topic 'Genomic aberrations/p53/HPV'.

While etiologic factors have been elucidated in recent studies, the pathogenesis of OE remains obscure. In particular, the question of whether OEs develop *de novo*, or whether an OL can change to an OE over time, has not been answered by the long-term follow-up studies as yet.

Shear[5] discussed in some detail why OEs appear red. It was suggested that one of the reasons was that the epithelium is thin and atrophic with a vascular lamina propria lying close to the surface. This alone, Shear argued, would not account for the diffuse redness of the lesion, particularly in areas where the epithelium is fairly thick. Shear assumed that the poorly differentiated epithelium might be more translucent than normal, an assumption which has never been substantiated.

Another aspect, which may have a role in the pathogenesis of OE, is infection with Candida. *Candida albicans* has often been demonstrated in erythroleukoplakia as secondary infection. After antifungal therapy the red component of these lesions and often the white component as well, diminishes or disappears.[48,49] Unfortunately, it is not yet known whether the red surface change in oral erythroleukoplakia (and nodular leukoplakia) is the result of inflammation, dysplasia, or both. No study has yet shown a positive correlation between the presence of dysplastic epithelium and candidal hyphae in homogeneous OE or carcinoma in situ.[26]

Histopathology

Over the years many attempts have been made to clinically classify each stage of the assumed spectrum from the 'true' (homogeneous), fiery red, velvety OE to the 'true' (homogeneous), thick white OL, resulting in suggesting several 'overlapping' terms as has been described above. Although the clinical terms have no specific histopathological connotation and should never be used as a microscopic diagnosis, there are hardly any reports available where the clinical and histological diagnoses have been compared or correlated.

One exception is the report by Shafer and Waldron[6] who studied a total of 65 biopsies from 58 cases (31 males and 27 females) of OE constituting 0.09% of 64,354 cases accessioned at two University Schools of Dentistry in Atlanta, USA. In order that the data from the two institutions are comparable, it was decided to include in this study *only* cases of OE of the homogeneous type (according to the classification suggested by Shear[6]). To assess the degree of epithelial dysplasia detected in the biopsies, the authors used the following three dysplasia categories: mild to moderate; severe to carcinoma in situ and carcinoma. Fifty-one percent were histologically diagnosed as invasive carcinomas, and 40% as carcinoma in situ or severe dysplasia. The remaining 9% showed mild to moderate dysplasia and, for this reason, there can be no consideration of 'high risk' and 'low risk' sites for homogeneous OE, since all sites seem to be high risk. Since this study dealt only with homogeneous OE, there is no information available for a clinicopathologic correlation of the different types of OE

or as to whether one is apt to be more serious than the others. However, the above facts should be of concern to the clinician and the pathologist alike. Mashberg[50] stated that based on about 500 oral mucosal biopsies, less than 2% of asymptomatic white (keratotic) lesions have been diagnosed as carcinoma or carcinoma in situ; whereas asymptomatic lesions with *erythroplastic* components often revealed malignant changes histologically. He concluded that *red velvety lesions with or without white components in high risk sites of the oral cavity should be considered at the very least carcinoma in situ or invasive carcinoma—unless proven otherwise*.

To this day, when precise clinical markers are still lacking, and with a controversial and confusing terminology as regards 'red and red-white' oral premalignant lesions, and in addition, recognizing that the assessing and grading of epithelial dysplasia is subjective and thus carries a low reproducibility, both clinicians and reporting histopathologists are indeed confronted with an enormous challenge. Warnakulasuriya[51] refers to The Epithelial Dysplasia Symposium held in London in 1997 where even after circulating the same photomicrographs, thus avoiding sampling error, discordant views were expressed on the individual grades assigned to the dysplasia by a panel of experienced oral pathologists. The wide intra- and inter-observer variability encountered in grading oral epithelial dysplasia corroborates with earlier studies in this field.[52–54] The author concludes that improving objectivity in reporting appears to be a key factor. A year earlier, the same author[55] when addressing the attempt having been made to apply molecular biological markers to oral premalignant lesions for the assessment of cancer risk, was not able to offer any consolation: ''Despite the impact of molecular diagnostics of tumours, assessing a patients risk for development of cancer of the oral cavity remains limited to 'H&E' pathology!''

Immunohistochemistry/ultrastructure

No immunohistochemical or ultrastructural studies of OE alone have been published. In contrast, however, numerous studies have been performed on epithelial atypia and dysplasia including carcinoma in situ. The interested reader is referred to this large body of information, the review of which is beyond the purpose of the present article. In summary, however, Warnakulasuriya[55] clearly stated that molecular markers including p53 to predict malignant potential of oral precancer were not available and that assessment of a patient's risk for development of cancer of the oral cavity remains limited to 'H&E' pathology.

Genomic aberrations/p53/HPV

Due to the rarity of OE few systematic studies of this particular oral precancerous lesion are available. Most often a small number of OEs is hidden away in studies on OL, a fact, which makes evaluation difficult. Recently, however, a few studies have been published with larger series of OE. One recent study focused on gross genomic aberrations of 57 dysplastic OEs in 37 patients using high-resolution image cytometry. Forty-one lesions of 25 patients were classified with aberrant DNA content (DNA aneuploidy), of which 23 patients (92%) later developed an oral carcinoma after a median observation period of 53 months (range 29—79 months). Of 12 patients having altogether 16 lesions with normal DNA content, none developed a carcinoma with a medium observation time of 98 months (range 21—163 months; $p < 0.001$). In a multivariate analysis, DNA content was a significant prognostic factor ($p < 0.001$), whereas histologic grade, gender, use of tobacco, size and location of the lesions, and the presence of multiple lesions were not.[56]

In another study[57] the p53 tumour suppressor gene (exons 5—9) were examined for mutations in 24 OEs with varying degrees of dysplasia using PCR/single-strand conformational polymorphism and direct DNA-sequencing analyses. A total of 12 p53 mutations were detected in 11 of 24 (46%) OEs. Thirty-three percent of lesions with mild dysplasia, 50% of lesions with severe dysplasia and 50% of lesions with carcinoma in situ showed p53 mutations. It was concluded that mutations of the p53 gene was linked to the high malignant potential of OE.

The role of human papillomavirus (HPV) in oral premalignant lesions has been discussed controversially during the recent years. Since in most studies on precancer cases of OE are under-represented, information about the role of HPV in OE is limited. One study[58] with 49 patients with potentially malignant oral lesions included 10 cases of OE (1 man, 9 women). The presence of HPV was studied immunohistochemically, by DNA—DNA in situ hybridisation and by PCR. Fifty percent of OEs were HPV positive and 33.3% of oral erythroleukoplakias. An overall HPV detection rate including all cases of premalignancy was 40.8%. The authors concluded

Table 2 Malignant transformation rates (%) for oral carcinoma in situ and/or severe epithelial dysplasia, ranked by rates

Author(s)	Country	Number of patients	Malignancy transformation rate (%)
Lumerman et al.[19]	USA	7	14.3[a]
Bouqout et al.[41]	USA[b]	32[c]	15.6[d]
Mincer et al.[59]	USA	16	18.8
Banoczy and Csiba[60]	Hungary	23	21.8
Vedtofte et al.[61]	Denmark	14	35.7
Silverman et al.[62]	USA	22	36.0
Amagasa et al.[63]	Japan	12[c]	50.0[d]
Total		126	26.3[e]

Lesions appeared clinically as red, white or combined red and white macules, i.e., not all were erythroplakias. Cancers not arising from the site of the precancer are excluded.
(Adapted from Bouquot and Ephros[26])
[a] Average follow-up time was less than two years.
[b] The only population-based study; represents middle-class whites.
[c] Includes only carcinoma in situ cases.
[d] Average follow-up time was 10 years or more.
[e] Weighed for different sample sizes.

that HPV may be an etiologic co-factor, because 100% of patients who developed oral cancer within 4—12 years were all positive for HPV, with one being HPV 16 positive.

Rate of transformation

Oral erythroplakia has the highest risk of malignant transformation compared to all other oral mucosal lesions at risk for transformation (oral leukoplakia, oral lichen planus, oral submucous fibrosis and others). The high risk for malignant transformation is based on the fact that on histology OE typically presents as carcinoma in situ, severe epithelial dysplasia or microinvasive carcinoma.[6,41] Transformation rates of oral precancerous lesions histologically diagnosed as carcinoma in situ or severe epithelial dysplasia including cases of OE but also lesions appearing as white (leukoplakia) or combined red and white (erythroleukoplakia) are shown in Table 2. Generally, transformation rates, including those with invasive carcinoma already at biopsy, vary from 14% to 50%.[26]

Differential diagnosis

Oral erythroplakia is a diagnosis of exclusion. Therefore, from the clinical point of view some diseases of the oral mucosa with red (erythematous) changes should be considered as differential diagnoses. Table 3 summarizes some of the red lesions of the oral mucosa that may be confused with OE.[5,17,27] Of these erythematous candidiasis and atrophic oral lichen planus are the most important. As has been stated by numerous experts in the field, biopsy is mandatory in cases of doubt.

Table 3 Red lesions resembling oral erythroplakia

(A) Mycotic infections
- Oral candidiasis
  - Erythematous candidiasis
  - Generalized candidal erythema
  - Denture-induced stomatitis
- Histoplasmosis

(B) Bacterial infections
- Tuberculosis

(C) Mucosal diseases
- Atrophic oral lichen planus
- Lupus erythematosus
- Pemphigus, Pemphigoids

(D) Others
- Amelanotic melanoma
- Haemangioma
- Telangiectasia, lingual varices
- Kaposi's sarcoma
- Oral purpura

Treatment and recurrence rate

Oral erythroplakias have been shown to have the highest risk for malignant transformation and therefore early effective treatment of such lesions is mandatory. The recommended treatment

for oral lesions at risk for malignant transformation has been surgical excision of lesions with severe epithelial dysplasia or carcinoma in situ and regular follow-up examinations of lesions which histologically show no to moderate epithelial dysplasia.[61,63] Since studies on treatment of OE alone are not available, literature on OL and associated epithelial dysplasia was consulted. In addition to 36 cases of OL Vedtofte et al.[61] studied 10 cases of OE and 15 cases of oral erythroleukoplakia for outcome after surgical treatment. Four cases of OE and three cases of oral erythroleukoplakia (40% and 20% respectively) recurred. Two cases of erythroleukoplakia underwent malignant transformation. Recently, results of an evaluation of surgical excision of non-homogeneous leukoplakia in a screening intervention trial (Kerala, India) including cases of erythroleukoplakia (2 of 59 cases) were published.[64] Malignant transformation was not observed in any of the cases ($n = 59$). 62.1% of patients were disease-free after three years. The authors came to the conclusion that the added value of specific treatments over and above primary prevention by tobacco and alcohol remains to be established. This was confirmed in a Cochrane database systemic review on interventions for treating OL.[65] This review showed that the possible effectiveness of surgical interventions, including laser therapy and cryotherapy, has until now never been studied by randomized controlled studies. In this study non-surgical interventions including vitamin A, retinoids, bleomycin, mixed tea and betacarotene were also reviewed. The reviewers came to the conclusion that to date there is no effective treatment in preventing malignant transformation of leukoplakia. Although, OE was not particularly mentioned, it may be assumed that the same conclusions would be true for this lesion with the highest risk for malignant transformation.

Few data on recurrence of EO are available. Amagasa et al.[63] recorded a recurrence of OE in 5 of 7 cases.

Educational issues

Only a few papers have been devoted to educational aspects relating to the ability to recognise precancerous lesions and conditions[66] and to OE in particular.[20] One experimental study on recognition of OE by undergraduate students revealed that sensitivity, specificity and agreement were higher in the specifically trained experimental group compared to a control group. It was suggested that teaching procedures using images of red lesions including OEs were effective.[20]

Conclusions

This review has clearly shown that the concept of OE has largely been neglected during recent decades and has developed into a complex and confusing issue. This may be explained by the fact that the overall terminology is inadequate and strongly needs updating or redefinition. The clinicians need clinical markers and the pathologists need improved objectivity in reporting for making accurate histological diagnosis and grading of oral epithelial dysplasia. It is believed that OE is a very rare lesion. That certainly may be correct if one focuses on the true, red homogeneous type of OE (as defined 30 years ago). However, if the clinical 'grey zone' of ill-defined red/white lesions is accepted under the cover of the 'OE-umbrella', the above statement may not be correct. Further, irrespective of the clinical definition of OE, it has been clearly documented that at least the homogeneous OE is the most dangerous precancerous oral lesion (showing the strongest malignant potential). OE is a much more worrisome lesion than leukoplakia, a lesion which earlier may have been—and still to a certain degree is—overemphasized. There is a tendency to retain elements of the leukoplakia concept, and use terms such as speckled leukoplakia, erythroleukoplakia, granular erythroplakia, and so forth. It is questionable whether this serves a useful end, since the proliferation of term adds to further confusion and reinforces the leukoplakia concept. Thus, there are several as yet unanswered questions, which are in addition to the above mentioned:

(1) Does OE develops *de novo* or does it have precursor lesions such as leukoplakia in its dierent clinical forms or other oral mucosal lesions?
(2) What is the possible role of Candida albicans and HPV co-infections in the development of OE? In this context, possible new findings of the role of HPV in the pathogenesis of penile erythroplakia (Queyrat) would be of interest.
(3) The biological behaviour of OE (whatever definition eventually may be chosen) should be studied in great detail.

Answers to the above questions may only be found based on large scale multicenter studies preferably in different geographical areas.

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