Clinical predictors of oral leukoplakia recurrence following CO_2 laser vaporization

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ABSTRACT

Objective: The objective of this study was to determine whether risk of early leukoplakia recurrence (within 3 months) following carbon dioxide (CO_2) laser removal varies by clinical characteristics including lesion size, site and accessibility of margins.

Materials and methods: A retrospective cohort study included patients with oral leukoplakia who had their first CO_2 laser surgery for removal of oral leukoplakia between 2005 and 2010 at the UCSF oral medicine clinic. Twenty-six patients with 32 separate lesions met the eligibility criteria after a clinic database search was followed by review of clinical notes and biopsy reports from existing patient charts. Data analysis included computation of summary statistics, and logistic regression analyses to evaluate recurrence of leukoplakia by clinical characteristics of the lesions.

Results: Patient data and the characteristics of lesions were evaluated as possible predictors of early recurrence following laser removal; these included age, sex, duration, size, appearance and histopathology of the lesion. The only one that reached statistical significance was poor accessibility of the margins of the lesion (vs. good accessibility, OR = 24.57 (95% CI: 1.59–16.68), $p = 0.016$); the probability for trend for good, questionable, and poor accessibility was 0.0028. This finding remained significant after controlling for age, sex, duration and size of lesion. Four out of five lesions with poor accessibility showed recurrence at 3 months. Of these, three involved the gingiva and one the lateral tongue.

Conclusions: This study has identified poor accessibility of the lesion margins as a predictor for early recurrence of leukoplakia following laser removal. Other variables evaluated did not reach statistical significance, possibly due to lack of power.

1. Introduction

'Oral leukoplakia is a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion' (Axéll et al., 1996). It is usually asymptomatic but may be associated with some degree of discomfort including sensitivity to spicy or acidic foods. It is a premalignant lesion for oral squamous cell carcinoma (OSCCA). The risk of malignant transformation has been reported as ranging from 0.13% to 2.2% per year in community-based cohorts in developing nations (Nappier and Speight, 2008), while higher risks have been reported from studies conducted in hospital-based tertiary clinics in developed countries, with 1.1%–17.5% of patients with leukoplakia developing OSCCA over varying follow-up periods (Nappier and Speight, 2008). The overall risk has been estimated to be about 1% per year (Petti, 2003; Van Der Waal,

2009), however, certain clinical features increase the risk for malignant transformation, including older age, longer duration, female sex, site (floor of mouth and lateral tongue are high-risk sites), speckled, nodular or verrucous appearance, greater size, and absence of risk factors such as smoking (Nappier and Speight, 2008). There is no proven safe and effective drug treatment for leukoplakia (Lodi et al., 2002, 2006). Published studies of surgical removal of leukoplakia have been mostly observational cohort designs. Surgical removal has not been evaluated in randomized controlled trials (RCTs), however it has been and currently is the most commonly used treatment approach for oral leukoplakia (Jerjes et al., 2012; Kumar et al., 2013; Mogedas-Vegara et al., 2015). Surgical approaches include the use of a scalpel for excision and/or use of a laser for excision and/or vaporization (for example: carbon dioxide [CO_2] laser [wavelength 10.6 μm]; Nd:YAG laser [neodymium-doped yttrium aluminum garnet, wavelength 1064 nm]; and (KTP) laser [potassium titanyl phosphate, wavelength 532 nm]). CO_2 lasers produce minimal thermal damage to underlying tissue, and have the advantage of decreased damage to adjacent structures as compared with other laser wavelengths. The advantages of CO_2 laser use include: a bloodless field preserving visibility, precise control, and improved healing with less scarring (Tambuwala et al., 2014). Therefore, this is a popular treatment approach for management of leukoplakia. A successful outcome following leukoplakia removal is healing of the surgical site with normal appearing mucosa. Post surgical recurrence occurs when the surgical site has completely epithelized, however white plaque-like change (leukoplakia) is clinically evident at the previously treated site.

The frequency of recurrence of oral leukoplakia after laser removal has been reported in several publications (Silverman, 1988; Roodenburg et al., 1991; White et al., 1998; Schoelch et al., 1999; Thompson and Wylie, 2002; Ishii et al., 2003; Van Der Hem et al., 2005; Lodi and Porter, 2008).

These estimates have been quite variable and have ranged from 9 to 38%. None of the reported estimates to our knowledge were stratified by lesion characteristics.

Our clinical observation is that this risk may vary based upon the clinical characteristics of the lesion, including the accessibility of the margins of the lesion for surgical removal and the size of the lesion. Furthermore, the risk factors for early recurrence may differ from the risk factors for late recurrence. Late recurrence may be related to individual etiologic factors (such as tobacco use and genetic factors); that is, the same factors which are responsible for causation of leukoplakia may be responsible for leukoplakia recurrence if not modified. However, some of these, such as genetic factors, are not modifiable. It is possible that early recurrence may be more influenced by local factors including lesion accessibility and other characteristics.

The objective of this study was to determine whether clinical/histopathologic characteristics may be predictors of early recurrence of leukoplakia following surgical removal. Availability of this information will allow individual patients and their clinicians to make more informed treatment decisions, and enable selection of cases for surgical intervention based on the lower likelihood of early recurrence.

2. Material and methods

2.1. Study design

A retrospective cohort study, involving a review of existing outpatient medical records was conducted in 2010. This study was approved by the Committee on Human Research which is the institutional review board at UCSF, San Francisco, CA, USA.

2.2. Study population

Patients with leukoplakia seen at the UCSF oral medicine clinic, who had CO_2 laser procedures conducted by or under the supervision of SS and/or NCW and had their first CO_2 laser procedure between 2005 and 2010 were possible candidates for the study. The CO_2 laser procedures were all conducted under local anesthesia using a continuous mode of operation of the laser, with depth extending into connective tissue or muscle depending on the site of the lesion. For extensive lesions more than one appointment was necessary for complete removal of the visible lesion.

The oral medicine clinic database was searched to identify potential patient charts using ICD-9 and CPT codes. ICD-9 diagnosis codes for leukoplakia, and CPT procedure codes for laser procedures and biopsies were used. This broad search strategy identified 235 clinic charts in the database which were reviewed. Twenty-six clinic charts of patients with 32 lesions who met the following eligibility criteria were included. Inclusion criteria: 1) clinical diagnosis of leukoplakia, 2) first laser surgery for leukoplakia at UCSF between 2005 and 2010. Exclusion criteria: clinic charts lacking sufficient detail to allow determination of the extent of lesions and/or recurrence of lesions.

Existing clinic records were reviewed to obtain the necessary data which included demographic information, tobacco and alcohol use, medical history, clinical information on size, anatomic site, accessibility of lesions, and histopathologic diagnosis at the time of the initial CO_2 laser procedure, as well as recurrence of leukoplakia after removal and malignant transformation. A total of 235 records were reviewed and 26 met the eligibility criteria (Fig. 1).

2.3. Categories for clinical characteristics

2.3.1. Size
Small: <1 cm^2 area; Large: <50% of site affected; Extensive: >50% of site affected.

2.3.2. Accessibility of margins
(1) Good: All margins accessible (e.g. localized lesion with all margins accessible, towards anterior aspect of mouth); (2) Questionable: >50% margins accessible (localized lesion towards posterior aspect of oral cavity with posterior margin not easily accessible/determined); (3) Poor: <50% margins accessible (gingival lesions with facial and palatal involvement, extensive lesions involving posterior aspect of oral cavity).

2.3.3. Appearance
(1) Leukoplakia; (2) Leukoplakia with nodular/verrucous appearance; (3) Erythroplakia; (4) Erythroleukoplakia.

2.3.4. Histopathology
(1) Hyperkeratosis with no dysplasia; (2) Dysplasia, mild-moderate; (3) Dysplasia, severe/carcinoma-in-situ; (4) Superficially invasive squamous cell carcinoma.

2.4. Statistical analysis

The distribution of continuous variables was described by mean and standard deviation, as well as by median and range. The distribution of categorical variables was described by frequencies and percentages.

Due to the small sample size, there was a perfect or almost perfect prediction of recurrence of leukoplakia among some groups which meant that estimates from regular logistic regression were invalid. Instead exact methods were used to avoid approximations that may be invalid with small numbers. Note that, in general, exact