

Oral leukoplakia remains a challenging condition

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Crispian Scully had many interests in the realm of oral diseases. But oral leukoplakia was one that piqued his curiosity when he was still an academic neophyte and remained a topic which he studied throughout his enormously productive career. It is easy to understand why. While the clinical manifestations of oral leukoplakia are common, we still do not fully understand why one version of the condition is benign, while another, similar in appearance, progresses to a malignancy. The diagnosis of oral leukoplakia is based on expert clinical and histopathological examination. Management and treatment of leukoplakia remain challenging especially for large lesions and the proliferative subtype. This review aims to provide a general overview on leukoplakia, explore current challenges in its diagnosis and management and discuss the opportunities to better understand the condition.

KEYWORDS

genomics, leukoplakia, management

1 | INTRODUCTION

In preparing this paper to honor and remember Crispian, we started by doing a PubMed search using two keywords: "Scully C and leukoplakia." No surprise, Crispian's writing on the topic was prolific—51 hits. But what was surprising was that his passion and interest in the topic were evident from his student days, especially with respect to the question of differentiating premalignant from malignant disease. True to form, Crispian's thinking was innovative. He recognized that leukoplakias varied widely in its premalignant/malignant potential, that such differences were biologically driven and that, consequently, molecular evidence (what we call biomarkers today) might have clinical utility in determining the risk of progression. His solo-authored manuscript entitled "Serum β_2 microglobulin in oral malignancy and premalignancy," published in 1981 described the results of a clinical study in which Crispian found that serum levels of β_2 microglobulin were elevated in patients displaying evidence of both oral carcinoma or keratosis/dysplasia (Scully, 1982). And like many of Crispian's concepts, the persistence of interest in the topic becomes a component of his legacy (Saddiwal et al., 2017).

Crispian's subsequent contributions on the topic of leukoplakia and, particularly the identification of biological differences between benign

and neoplastic forms of the condition and potential clinical methods to define the two spanned his career. His passion and persistence for the subject are reflected by the title of the lead Anniversary Review he wrote for this journal in 2014: Challenges in predicting which oral mucosal potentially disease will progress to neoplasia (Scully, 2014). The conclusions he notes in the manuscript remain relevant and critical today: "Probably the greatest challenge to those managing patients with oral diseases is the dilemma of attempting to predict which oral erythroplakias, leukoplakias, lichenoid and other potentially malignant mucosal disease...will progress to neoplasia." As we review below, Crispian's vision, innovation, teaching, and writings have influenced the progress within this space.

2 | LEUKOPLAKIA: A CLINICAL ENTITY

Leukoplakia as defined by the World Health Organization (WHO) is a "white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer" (Warnakulasuriya, Johnson, & van der Waal, 2007). Leukoplakia is a clinical term which is typically modified based on histopathological examination. The pooled prevalence estimated for leukoplakia of

the oral cavity is between 1.5% (1.4%–1.6% 95% confidence interval [CI]) and 2.6% (1.7%–2.7% 95%CI) with no gender predilection (Petti, 2003). The risk factors associated with oral leukoplakia are similar to those for oral cancer and include tobacco smoking, heavy alcohol consumption, betel nut chewing, old age and UV light exposure (for lesions of the lip) (Arduino, Bagan, El-Naggar, & Carrozzo, 2013; Petti & Scully, 2006).

Clinically, different forms of leukoplakias exist; homogeneous leukoplakia is characterized by a flat and uniform white plaque with well-defined margins (at least one). Non-homogeneous leukoplakia presents with areas of erythema accompanied by areas of nodularity and verrucosity (van der Waal, 2010). Oral proliferative verrucous leukoplakia (PVL) is a distinct subset of non-homogenous leukoplakia. PVL may involve a single large site, but is frequently multifocal and often occurs on the gingiva, buccal mucosa, and tongue in both contiguous and non-contiguous sites of the oral cavity (Bagan, Scully, Jimenez, & Martorell, 2010; Bagan et al., 2003; Pentenero, Meleti, Vescovi, & Gandolfo, 2014; Warnakulasuriya et al., 2007). Of note, PVL is more common in females and is usually not associated with tobacco smoking.

The diagnosis of oral leukoplakia is based on expert oral clinicopathologic examination. PVLs or large leukoplakias require multiple periodic biopsies at different site to detect different grades of dysplasia or oral squamous cell carcinoma (OSCC) (Villa & Woo, 2017). Approximately 10%–17% of cases may be missed if only a single biopsy is obtained (Lee et al., 2007; Pentenero et al., 2003).

3 | THE MALIGNANT TRANSFORMATION OF ORAL LEUKOPLAKIA

The malignant transformation rate of leukoplakia varies depending on the type of leukoplakia considered. Homogenous leukoplakias have a lower risk of transformation (0.6%–5%) compared to the non-homogeneous cases (20%–25%) (Napier & Speight, 2008; Reibel, 2003; van der Waal & Axell, 2002). PVL is the most aggressive entity with a malignant transformation rate of 61.0% over an average follow-up period of 7.4 years with an overall 40.0% mortality rate (Abadie, Partington, Fowler, & Schmalbach, 2015; Pentenero et al., 2014). The oral sites associated with a higher risk of dysplasia and/or cancer are the ventral tongue, floor of the mouth, and soft palate (Scully, 2014; Warnakulasuriya & Ariyawardana, 2016). Large lesions ($\geq 200 \text{ mm}^2$) are five times more likely to undergo malignant transformation (Holmstrup, Vedtofte, Reibel, & Stoltze, 2006).

Previous studies have shown that the malignant transformation rate of dysplasia or carcinoma in situ (CIS) is 5%–36%, with higher rates in individuals who consume betel leaf (Cowan, Gregg, Napier, McKenna, & Kee, 2001; Hsue et al., 2007; Lian le, Tseng, Su, & Tsai, 2013; Liu et al., 2012; Lumerman, Freedman, & Kerpel, 1995; Silverman, Gorsky, & Lozada, 1984). When “hyperkeratosis without dysplasia” (or keratosis of unknown significance (KUS)) was considered, 11%–30% of cases developed invasive carcinoma (Holmstrup et al., 2006; Lee et al., 2006; Roed-Petersen, 1971; Scully, 2014).

4 | FROM LEUKOPLAKIA TO ORAL SQUAMOUS CELL CARCINOMA

Leukoplakia is thought to progress from hyperkeratosis or hyperplasia (or the so called KUS) (Woo, Grammer, & Lerman, 2014), to various degrees of dysplasia (mild, moderate, and severe), and ultimately carcinoma in situ and/or OSCC (Lumerman et al., 1995; Warnakulasuriya et al., 2007). The presence of dysplastic areas in the epithelium of the oral cavity has been associated with an increased risk of malignant transformation. While many leukoplakias are outright dysplasias or invasive SCCs at the time of biopsy, several non-dysplastic keratotic lesions (KUS) also transform to invasive carcinoma over time. In 1984, Silverman et al. showed that 16% of patients with oral “benign hyperkeratosis” underwent malignant transformation (Silverman et al., 1984). Similarly, in a study by Schepman, van der Meij, Smelee, & van der Waal (1998) patients with leukoplakia with a histopathological diagnosis of “benign hyperkeratosis” developed OSCC in 30% of the cases.

The evolution from dysplasia to invasive cancer is not yet well understood. A key step to improving oral cancer outcomes is to identify the molecular factors driving disease initiation and progression, as these factors may represent good candidates for targeted therapies. To date, there have been a few molecular studies to outline these factors in oral leukoplakia and oral cancer (Banerjee, Bhattacharyya, & Vishwanatha, 2005; Garnis et al., 2009; Sumino et al., 2013). In the past few years, there has been an increasing interest in genes that predispose to oral carcinogenesis from oral leukoplakia. In particular, recent studies have shown that genetic analysis may be promising in predicting the malignant progression of oral leukoplakias (Bremmer et al., 2011; Saintigny et al., 2011). The identification of risk-predicting genes related to the malignant transformation may play a significant role in determining an individual's risk of developing cancer and therefore guide treatment decisions.

Oral dysplasias are associated with a significant rate of malignant transformation (5%–36%) (Cowan et al., 2001; Hsue et al., 2007; Lian le et al., 2013; Liu et al., 2012; Lumerman et al., 1995; Silverman et al., 1984), yet the underlying molecular mechanisms and pathways involved in oral cancer development have not been fully elucidated (Warnakulasuriya & Ariyawardana, 2016). Recent research suggests that the progression from dysplasia into invasive cancer, based on models established at other sites (e.g., melanoma and cervical cancer), involves a stepwise accumulation of genetic and epigenetic alterations (including somatic gene mutations, DNA double-strand breaks, and copy-number alterations) (Cervigne et al., 2014; Jessri, Dalley, & Farah, 2017; Vogelstein & Kinzler, 2015). The main steps that lead to the development of cancer include a breakthrough phase, an expansion phase, and an invasive phase (Kuffer & Lombardi, 2002; Vogelstein & Kinzler, 2015; Woo, Cashman, & Lerman, 2013). During the breakthrough phase, a very specific mutation occurs and the cell begins to divide abnormally. The lesion (e.g., leukoplakia) becomes visible only after a few years. In the second phase, an additional driver-gene mutation develops to give rise to the tumor. Finally, during the third phase the tumor invades the surrounding tissues. Leukoplakia

may share some of the same driver-gene mutations observed in OSCC and carry similar chromosomal instability, such as loss of heterozygosity, DNA aneuploidy, and telomerase dysfunction, which have all been associated with malignant transformation (Oulton & Harrington, 2000; Sen, 2000; Siebers et al., 2013). Approximately 20%–45% of oral epithelia dysplasia showed DNA aneuploidy with a higher prevalence in more severe dysplasias and in those lesions that underwent malignant transformation (Donadini et al., 2010; Gouvea et al., 2013; Torres-Rendon, Stewart, Craig, Wells, & Speight, 2009). Studies have shown that telomerase activity was upregulated with increasing grade of oral dysplasia, indicating an important role of telomerase hyperactivation in carcinogenesis (Liao, Mitsuyasu, Yamane, & Ohishi, 2000; Miyoshi et al., 1999).

Aberrant expression of p16INK4a, p53 (Angiero et al., 2008; Nasser, Flechtenmacher, Holzinger, Hofele, & Bosch, 2011; Pitiyage, Tilakaratne, Tavassoli, & Warnakulasuriya, 2009) and mutations of genes on 3p, 9p, 11q, and 17p (particularly TP53) may be associated with an increased cancer risk (Califano et al., 2000; Graveland et al., 2013). In addition, DNA hypermethylation at specific loci (such as CDKN2A, CDH1, and MGMT) has been detected in both oral dysplasias and OSCC with altered expression of miRNAs (such as miR-345, miR-21, and miR-18b), which have been associated with the progression of oral potentially malignant disorders (including leukoplakia) (Brito, Gomes, Guimaraes, Campos, & Gomez, 2014; Kato et al., 2006; Kulkarni & Saranath, 2004).

More recently, preclinical data suggested that immune modulation plays a critical role in oral carcinogenesis (Ferris, 2015). With recent advances in immuno-oncology demonstrating the efficacy of immune checkpoint inhibitors targeting the programmed cell death protein-1 (PD-1) axis in advanced squamous cell carcinoma of the head and neck (Chow et al., 2016; Ferris et al., 2016), there is significant interest in understanding the impact of anti-PD-1 therapy in early OSCC and in cancer prevention. A recent study from Yagyu et al. (2017) suggested that nearly 50% of high-grade oral leukoplakia samples were ligand of PD-1 (PD-L1) positive. Moreover, PD-L1 positivity and CD8 + T-cell count were significantly associated with the degree of dysplasia among these samples ($p < .001$). These findings suggest that antitumor immunity may be suppressed through upregulation of PD-L1 among leukoplakia lesions, which could promote oral carcinogenesis.

5 | MANAGEMENT OF ORAL LEUKOPLAKIA

Management and treatment of leukoplakia remain challenging especially for large lesions and PVLs. Often times, patients present with multifocal non-contiguous lesions (PVL) with a histopathological diagnosis of “hyperkeratosis no dysplasia,” yet 70%–100% will develop cancer over time. Current strategies for oral leukoplakia include surgery, a “watch-and-see” approach, and medical treatment (Farah et al., 2014; Lodi et al., 2016; Ribeiro, Salles, da Silva, & Mesquita, 2010). Recurrence after surgical excision ranged from 0% to 35% (Holmstrup et al., 2006; Lumerman et al., 1995; Pindborg,

Jolst, Renstrup, & Roed-Petersen, 1968; Silverman et al., 1984; Vedtofte, Holmstrup, Hjorting-Hansen, & Pindborg, 1987); 0%–15% when carbon dioxide laser was used; and 10%–25% in patients who underwent photodynamic therapy (Vohra et al., 2015). As a result of multiple recurrences post-treatment, several topical agents for oral cancer chemoprevention have been tested in the past decades (Chau et al., 2017). In particular, topical retinoids, bleomycin, adenovirus, cyclooxygenase inhibitors, and phytochemical-enriched agents have been used for oral leukoplakias. A recent systematic review has shown that the mean complete response rate for topical retinoid therapy was 32% (Chau et al., 2017), for 1% bleomycin was 40.2%, and for 0.5% bleomycin was 25%. However, all of these agents were once again associated with recurrence of the disease.

6 | CONCLUSION

Crispian was a translational scientist who recognized and advocated for the integration and application of advances in cell biology into the field of oral medicine. He specifically recognized the opportunity and potential of genetic signatures for leukoplakia, and genotyping or biomarker analysis in predicting which leukoplakias were most likely to transform (or not) to invasive cancer. But perhaps most importantly, Crispian never forgot the importance of the role of the front-line clinician in decision-making and the responsibilities associated with providing patients with the most valid information on which to make treatment choices.

AUTHOR CONTRIBUTIONS

Dr. Alessandro Villa was involved with the conceptualization, methodology and papers review. He wrote the original draft/manuscript and is accountable for all aspects of the work. Dr. Stephen T. Sonis was involved with the conceptualization of the paper. He critically reviewed and edited the manuscript. He approved the final version to be published.

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