Dermatology Practical & Conceptual

Mucosal Cancers Arising in Potentially Malignant Lesions of the Oral Mucosa Are Marjolin Ulcers: New Insights Into Old Concepts

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ABSTRACT

Introduction: Several disparate mucocutaneous diseases present oral mucosal lesions that have been classically labeled as "pre-cancerous", "pre-malignant", or "potentially malignant". These include oral lichen planus, dyskeratosis congenita, tertiary syphilitic glossitis chronic graft-versus-host-disease, and oral discoid lupus erythematosus. There is much confusion in literature regarding the real malignant potential of these oral lesions in relation to the incidence of squamous cell carcinoma.

Objectives: We tried to unify the occurrence of squamous cell carcinoma in some oral mucosal diseases into the classic concept of "Marjolin ulcer".

Methods: We analyzed the most relevant published evidence of the occurrence of squamous cell carcinoma arising in oral lichen planus, dyskeratosis congenita, tertiary syphilitic glossitis chronic graft-versus-host-disease, and oral discoid lupus erythematosus, and tried to establish a logical link between them.

Results: Reported cases of squamous cell carcinoma occurring in oral lesions of these diseases seem to appear in old standing, scarring lesions.

Conclusions: Oral lichen planus, dyskeratosis congenita, tertiary syphilitic glossitis, chronic graft-versus-host-disease, and oral discoid lupus erythematosus are not "pre-malignant diseases", their long-lasting mucosal scars are prone to the development of squamous cell carcinomas. In this sense, this tumor can be considered a mucosal type of Marjolin ulcer.

Introduction

There are several mucocutaneous diseases whose oral lesions have been classically labeled as "pre-cancerous", "pre-malignant", or "potentially malignant" [1]. Among these, the most frequently remembered are oral lichen planus (OLP), dyskeratosis congenita (DC), and tertiary syphilitic glossitis [2-4]. In some others, such as chronic graft-versus-host-disease (GVHD), and lupus erythematosus, some publications report an increased incidence of malignancies [5,6].

There is much of confusion in dental and dermatologic literature regarding the real malignant potential of these oral lesions in relation to the incidence of squamous cell carcinoma (SCC) and the possible mechanisms involved in the "transformation or "malignization" [1]; there is no satisfying unifying concept about these issues.

The eventual onset of SCC on in areas of vicious healing and sequelae of different cutaneous diseases has long been described and recognized by dermatologists; the tumors that issue under these particular circumstances are known as "Marjolin ulcers" [7]. Examples include sequelae of burns, osteomyelitis, discoid lupus erythematosus, chromoblastomycosis, hidradenitis suppurativa, porokeratosis, lupus vulgaris, and epidermolysis bullosa dystrophica [6,8-12].

The exact mechanisms by which SCC appears on these cutaneous sequelae have not been totally elucidated. Some authors believe that chronic scarring, in combination with constant local inflammatory stimuli, might be associated with carcinogenesis [6]. Recently, analysis of a lesion of SCC appearing in a case of discoid lupus erythematosus (DLE) revealed a null-type pattern of p53 protein expression and abundant CD123+ plasmacytoid dendritic cells, as potential drivers of oncogenesis and inflammation [13].

Objectives

In this commented review, we try to unify the occurrence of SCC in some oral mucosal diseases into the classic concept of "Marjolin's ulcer".

Methods

We analyzed the most relevant published evidence of the occurrence of SCC arising in some disparate chronic oral mucosal diseases. Relevant literature about cancer occurring in lesions of oral lichen planus, oral mucosal graft versus host disease, dyskeratosis congenita, oral mucosal lupus erythematosus and oral mucosal syphilis was searched, as well as some of previous studies by our group. We tried to establish a logical link between the occurrence of cancer in these entities. Consent from patients whose pictures were included have been obtained.

Results

Oral Lichen Planus (OLP)

Cutaneous lichen planus (LP) is generally self-limited, almost always occurring in outbreaks; OLP more commonly tends to be chronic and persistent if untreated [15]. In this way, OLP may develop cicatricial sequelae, similar to what occurs with other protracted forms of the disease, such as ungual LP (anonychia) and scalp LP (alopecia) [14].

If patients with persistent OLP are followed-up for many years, one observes the frequent development of mucosal atrophy, tongue depapillation, leukokeratotic scars, and even synechiae affecting the gingival sulcus or the lingual frenulum.

Several studies tried to associate an alleged increased risk of "malignant transformation" of OLP lesions into SCC. This "risk" ranges from 0.4% to 5%, with observation periods varying from six months to 20 years [2,15]. Another review proposed a range from 0% to 5%, highlighting the risk of "erythematous and erosive lesions". These authors studied 15 previous publications with average follow-up period of 8.9 years. They acknowledge, though, that criteria in diagnosing lichen planus and SCC among these studies was not uniform [16].

A study with 303 patients with OLP followed for many years revealed seven cases of SCC; patients with OLP were 4.8 times more likely to have OSCC than the matched referents [17].

Our group recently reported eight patients with histologically confirmed SCC in association with OLP in a group of 201 OLP patients [18]. In all eight, OLP had been present for many years. SCC only appeared in cases of long-lasting OLP with the presence of cicatricial sequelae in the mucosa (Figure 1, A and B).

SCC is very rare in association with cutaneous LP, as the latter seldom develops cicatricial sequelae, but it can occasionally occur in rare protracted cases [19]. The occurrence of SCC in scars of ungual LP has been recently reviewed [20].

Lichenoid GVHD

GVHD occurs in 25% to 40% of patients who underwent hematopoietic stem cell transplantation after a long period of follow-up [5].

Chronic lichenoid GVHD disease is clinically very similar to LP, and oral lesions of GVHD are indistinguishable from OLP, including tendency to induce mucosal scarring and sequelae [5].

SCC is known to rarely occur in association with oral lesions of GVHD. A recent review of 81 published patients showed that the mean time from oral GVHD development and "transformation" to SCC was 86 months, with the longest "transformation" time being 22 years [5].

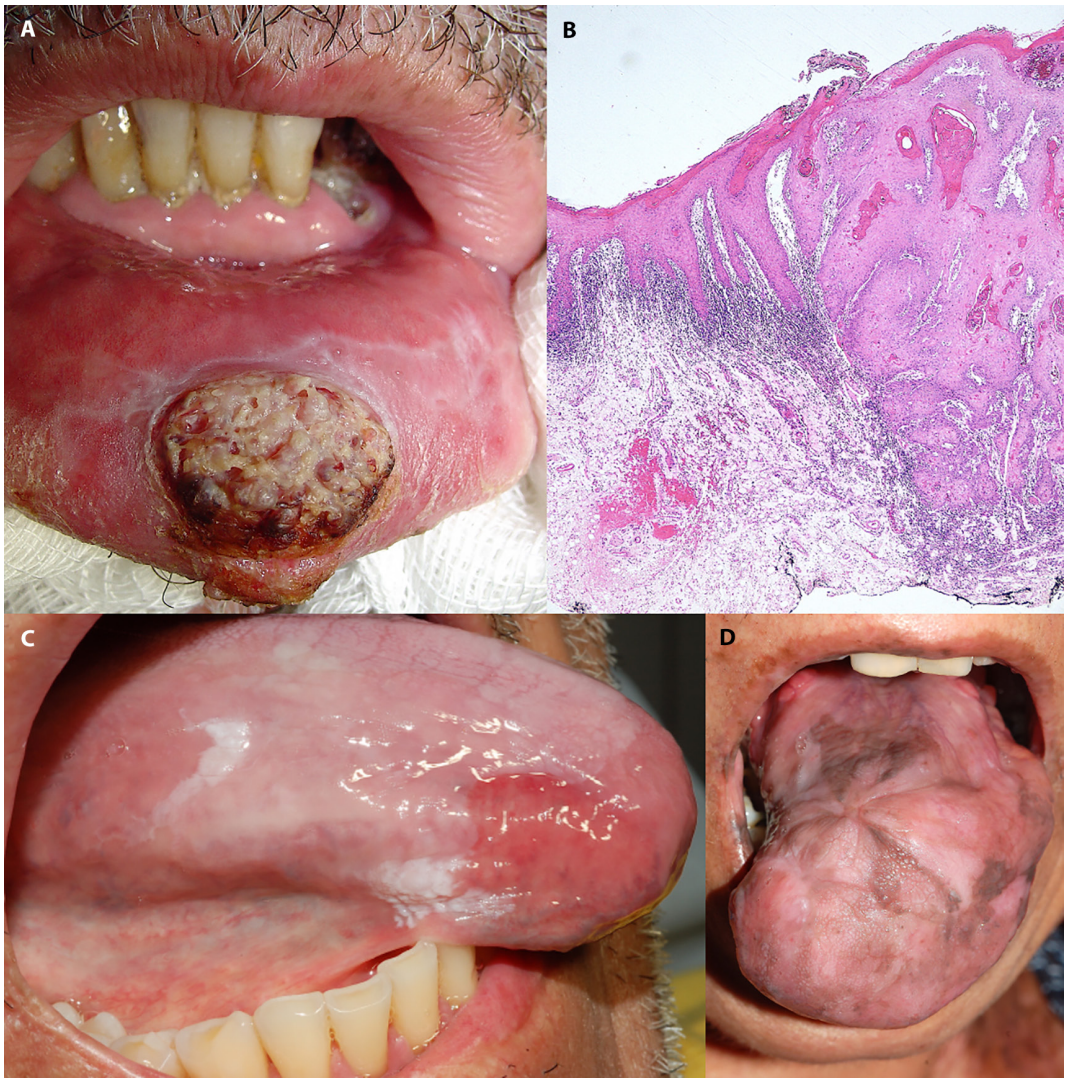

Figure 1. (A) Verrucous mass diagnosed as squamous cell carcinoma (SCC) in the center of a longstanding atrophic patch of oral lichen planus (OLP) in the inner lip mucosa. (B) Histopathology of a case of concomitating OLP and SCC. On the left there is interface mucositis; on the right there is a well-differentiated, invasive SCC (H&E, 40X). (C) A red, eroded lesion histologically diagnosed as superficial SCC occurring in a leukokeratotic and scarring patch in a patient with chronic lichenoid graft-versus-host-disease (GVHD). (D) Poikilodermal aspect of the tongue surface in a patient with treated chronic lichenoid GVHD. The large scar is due to surgical removal of a SCC.

The authors concluded that "The transformation time was shown to be varied, however, there were no important relationships with drugs or harmful habits that would indicate an influence on transformation times. The classic etiological factors associated with oral SCC in non-transplanted patients, smoking and alcohol do not seem to play an important role in oral carcinogenesis in areas of GVHD", although they considered that "such as the states of prolonged inflammation of the oral mucosa combined with the use of immunosuppressive drugs and cellular genetic mutations" may be important.

As in OLP, SCCs in association with GVHD seem to occur almost only in chronic, cicatricial lesions (Figure 1, C and D).

Chronic Discoid Lupus Erythematosus (Figure 2, A and B)

The occurrence of SCC in cutaneous DLE has been recently reviewed [6]. A total of 118 published patients were analyzed: the majority were males, localized DLE was present in 73.7% of the patients, and generalized DLE (DLE lesions below the neck) was present in 21.2%; 5.1% did not report DLE distribution. The most common sites of SCC development were the lip (53.3%), forearm (11.5%), and scalp (7.4%). The lower lip (41.8%, N = 51/122) was more affected than the upper lip (11.5%, N = 14/122). The average duration between DLE onset and SCC development was 15.0 years.

A recent study reviewed 22 published cases of SCC appearing over labial (22 cases) and oral mucosal lesions

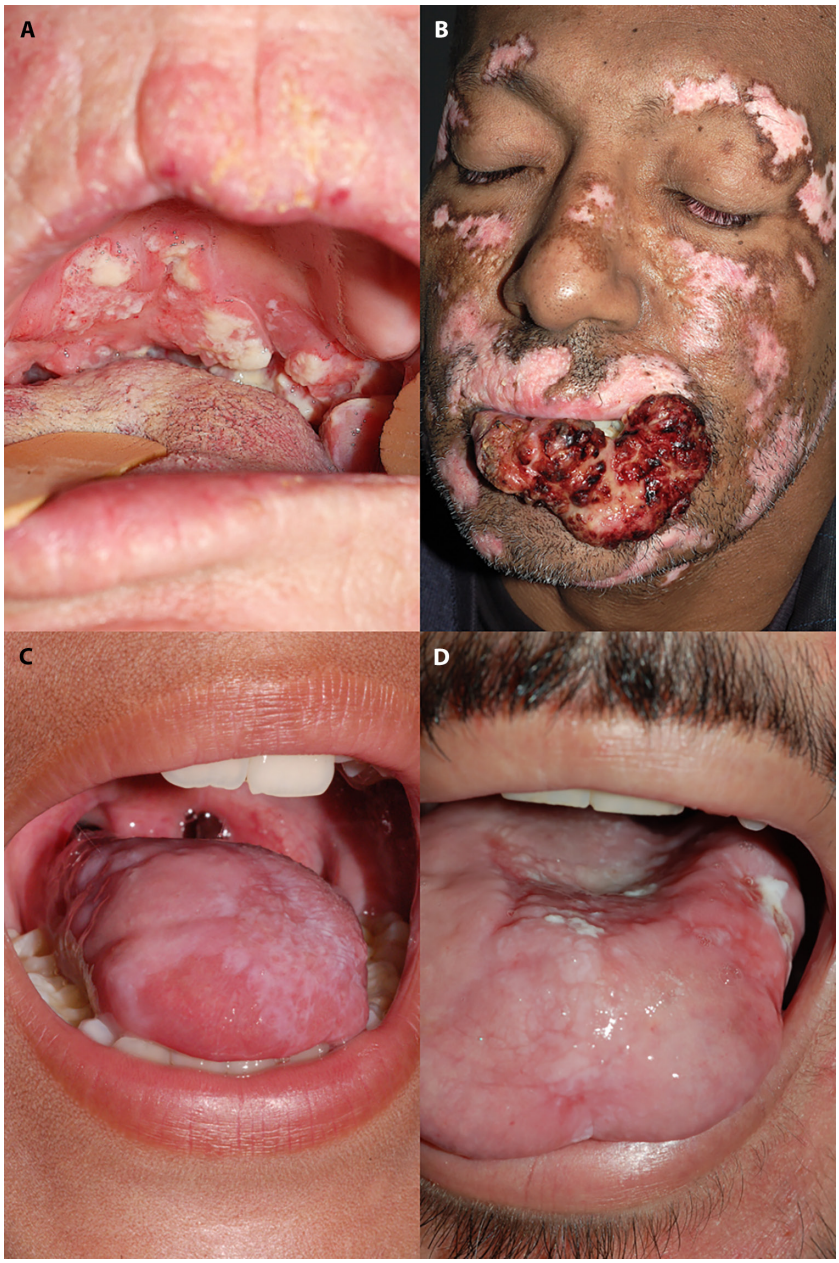

Figure 2. (A) A 65-year woman with long-standing discoid lupus erythematosus (DLE) had lesions on the lips and palate. squamous cell carcinoma (SCC) developed associated to palatal lesions. (B) Exuberant atrophic cicatricial sequelae due to DLE on the face and lips. A vegetating SCC developed on the lower lip. Notice that the patient is dark skinned; a lower lip SCC should be unexpected. (C) A 9-year-old boy presenting the first signs of DC. Peri labial delicate, reticulated pigmentation, and erosions on the tongue surface. (D) The same patient after 12 years presenting extensive atrophy of the tongue surface as well as depapillation. An ill-defined, infiltrated mass developed on the left posterolateral area of the tongue. An invasive SCC was diagnosed on histopathology.

(1 case) of DLE. Time of disease until development of SCC varied from 2 to 39 years (average 17 years) [21].

A SCC developing in a scarring lesion of periungual DLE has been recently described [22]. What all these studies have in common is that they show that SCC develops only in old scars of DLE, and not on the non-scarring lesions of acute or subacute lesions of LE.

Dyskeratosis Congenita

Dyskeratosis congenita (DC) is a multisystem inherited syndrome characterized by mucocutaneous lesions, bone marrow failure, and predisposition to cancer. DC is mainly considered a disease of defective telomere maintenance and patients usually have very short telomeres. Tissues with cell populations that must regenerate frequently are most

affected in DC. Features of DC usually appear in late childhood [3].

DC is better understood as a genetically mediated phenomenon that ultimately leads to epithelial scarring, representing the phenotypic expression of the cellular defect [23].

DC mucocutaneous lesions begin with interface inflammation that ultimately leads to mucocutaneous scarring and poikiloderma [23,24]. Cutaneous lesions include reticulated pigmentation (poikiloderma) and nail atrophy leading to anonychia.

On oral tissues, superficial erosions are first seen, slowly followed by progressive tongue depapillation and atrophic/ hyperkeratotic white scars along the mucosa (wrongly named "leukoplakia") are observed [23].

Oral squamous cell carcinoma (SCC) may develop in up to 35% of cases [3,25], and invariably appears is areas of intense areas of chronic mucosal scarring (Figure 2, C and D), and not from "transformation from leukoplakia", as classically stated on literature. This complication seems more related to mucosal scarring than to the DC gene mutations, that more usually lead to hematologic cancer.

Syphilis

In the early XX century it was recognized that patients who presented with carcinoma of the tongue had a high incidence of syphilitic infections. During the 1920s and 1930s patients with carcinoma of the tongue were 3-5 times more likely to have syphilis than random patients. This association was largely confined to patients with carcinoma of the tongue, and not at other sites [26].

In ancient textbooks, syphilitic tertiary glossitis was considered prone to "malignant transformation" (Figure 3A).

In a 1995 study, five of the 63 patients (8%) who presented with SCC of the tongue reacted to syphilis antibodies, but no mention was made about the presence of previous oral syphilitic gumme [26].

The wrongly named syphilitic "leukoplakia" is extremely rare today. It is considered a cicatricial sequel of a syphilitic gumma of the tongue (tertiary syphilis) [4]. Clinically one sees areas of persistent leukokeratosis and scarring on the tongue surface We have seen only one of such cases (Figure 3B). After a few years, a SCC developed in association within the cicatricial area (Figure 3C).

Conclusions

The pathological situation on where there is persistent and continuous lymphocytic attack against the basal layer of the epidermis will produce, over time, thinning of the epithelium and changes in the superficial dermis characterized by telangiectases, presence of melanophages and fibrosis. Clinically, these changes present as cutaneous atrophy, telangiectases, pigmentation, poikiloderma, cicatricial alopecia and irreversible nail changes resulting in *pterygium unguis* and anonychia. This is variably seen in diseases characterized by persistent interface inflammation such as dermatomyositis, lupus erythematosus, mycosis fungoides, chronic GVHD, and even in poikilodermal genodermatoses such as DC and Rothmund Thomson syndrome. This also may occur in cases of persistent cutaneous lichen planus. These sequelae are not seen in cases of acute/ self-limited interface diseases such as acute/subacute lupus, drug eruptions, erythema multiforme, paraneoplastic pemphigus and the usual forms of cutaneous lichen planus [27].

The common point of the oral mucosal diseases discussed here is their chronicity and propensity to produce sequelae that manifest clinically as mucosal atrophy, persistant tongue depapillation, and at times, sinequiae. In the cases of OLP, GVHD, DLE, and DC, these sequelae occur as consequence of persistent interface inflammation, in the same fashion that occurs in their cutaneous counterparts [27]. We could not find any accurate description of the histopathological findings of the sequelae of syphilitic glossitis, since it is so rare these days, but it is certain that this process produces significant cicatricial sequelae as well.

The mucosal sites on where SCC related to chronic mucosal diseases appear are frequently distinct from the classical sites of SCC in the mouth (such as floor of the mouth, lateral tongue, and soft palate). SCC related to chronic oral diseases more frequently compromise the tip and back of tongue, the gums, and the buccal or lip mucosa, at the site of ancient lesions. In the case of DLE, sun-exposure on a cicatricial discoid patch on the lower lip can be an additional factor leading to SCC, but cases on the upper lip (less-sun-exposed) affected by DLE are also described, suggesting that other predisposing factors may be involved [21].

It became evident in studying the presence of SCC in these oral diseases that this tumor arises only in longstanding cases with mucosal sequelae. It seems reasonable to suppose that the epithelium with cicatricial changes is the site on where SCC occurs in this situation. We have paid particular attention to this detail in our observations, in contrast to previous authors [14,18,20-22].

In this way, we consider that the tendency of a previous mucosal lesion be a site of SCC is not directly to the disease itself, but due to their scars. In this sense, in the same fashion that is defined on the skin, these SCCs represent "mucosal Marjolin ulcers".

We have mentioned this idea in previous publications, but this is the first time it has been presented in a unifying concept. On the other hand, some other questions still arise [14,18,20,22]. The exact mechanisms why mucocutaneous

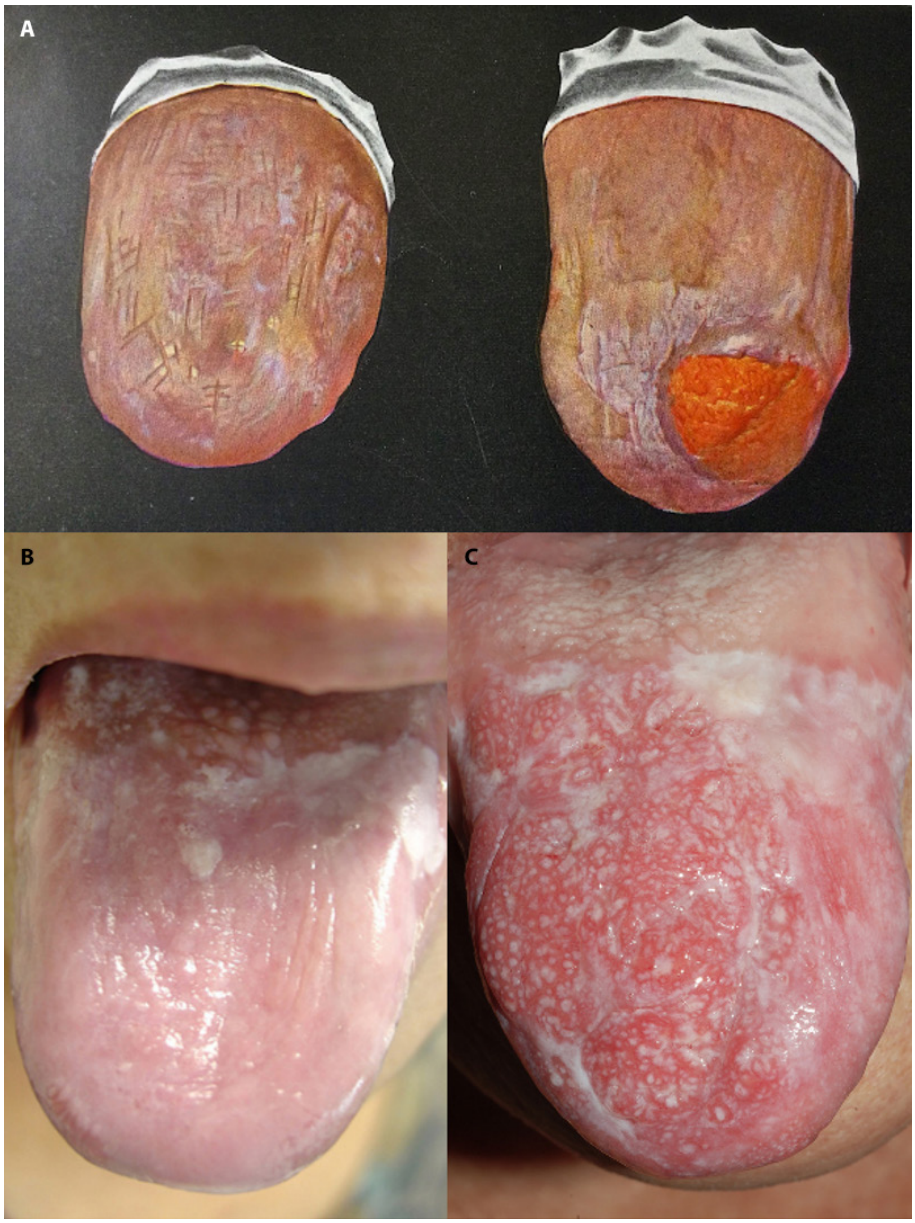

Figure 3. (A) syphilitic "leukoplakia" and "epithelioma" (from E. Gaucher 's "Le Chancre et Les Syphilides Cutanés et Muqueuses" A. Octave Doin, Editor, 1907), (B) A 70-year-old female patient presented an extensive leukokeratotic and scarring patch on the back of the tongue. She had been treated for tertiary syphilis some years before. (C) she was lost follow-up, and was re-examined after a few years; a vegetating, friable mass had developed on the cicatricial patch. Squamous cell carcinoma was confirmed on histopathology. This patient presented the same disease sequence as depicted on panel.

scars predispose to SCC are still unknown [6,13]. Furthermore, we cannot explain why in some diseases SCC is seen more frequently in mucosal sequelae than in the skin affected by the same scarring processes, as occurs in GVHD, DC, and tertiary syphilis.

In conclusion, what OLP, chronic GVHD, DLE, and DC have in common is the appearance of sequelae induced by persistent interface mucositis. These entities, including the mucocutaneous manifestations of DC, are inflammatory in nature, and essentially should not be considered "premalignant" [23,24]; on the other hand, their long-lasting scars are certainly prone to the development of SCC, as are many other scarring skin diseases ("Marjolin ulcer"). It is important that these patients are monitored long-term, even if disease activity appears controlled. This theory is based on previously published cases as well as on our own experience with the mentioned diseases, and it attempts to establish a parallel in the oral mucosa with the classic concept of Marjolin ulcer of the skin.

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