Desquamative Diseases and Periodontal Health/Treatment

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Abstract

Purpose of review: The purpose of the present review is to answer the following focused question: “What are the most relevant findings about the diagnosis and subsequent treatment of desquamative gingivitis (DG)?”

Recent findings: Topical corticosteroids in the form of gel should be the first-line medical treatment and may be sufficient for some moderate or mild forms of DG. When patients continue to experience erosions and pain despite topical therapy, treatment with systemic therapy is indicated. A tailored plaque control program is effective in reducing gingival manifestations of DG in terms of related symptoms, plaque index, mucosal disease score, gingival crevicular fluid volume, matrix metalloproteinase (MMP)-1 and MMP-9.

Summary: The painful symptoms and clinical features in gingiva are improved by non-traumatic oral hygiene procedures, but the underlying causes of DG cannot be eliminated by plaque control alone. Thus, the cooperation with dermatologists/oral pathologists is always required. New technologies for home oral hygiene may improve patients’ quality of life.

Introduction

Background

Desquamative gingivitis (DG) is an unspecific descriptive term that defines a clinical condition of the gingiva caused by a variety of pathological entities. DG is used to indicate epithelial desquamation, erosion, redness, and/or vesiculo-bullous lesions of the attached and marginal gingiva usually associated with pain and discomfort for the patients [1]. The new Classification of Periodontal and Peri-Implant Diseases and Conditions, which was redacted in occasion of the 2017 World Workshop of Periodontology, maintained the distinction between dental biofilm-induced gingivitis and non-dental biofilm-induced inflammatory gingival conditions [2***]. The first is defined at the site level as an inflammatory lesion resulting from interactions between the microbial plaque and the host immune-inflammatory response, which remains confined to the gingiva. Such inflammation can be reversed by effective home oral hygiene practices. Non-dental biofilm-induced inflammatory gingival lesions can be the oral manifestation of a variety of pathological entities and usually do not resolve following microbial plaque removal alone (Table 1). Several mucocutaneous disorders, such as oral lichen planus (OLP), mucous membrane pemphigoid (MPP), pemphigus vulgaris (PV), erythema multiforme (EM), lupus erythematosus (LE), drug-induced lesions, together with hypersensitivity reactions, may present in the oral cavity in the form of DG. Besides their heterogeneity, they share an immune-mediated pathogenesis and may not be completely reversible after treatment.

DG is a clinically relevant entity as it is often a clinical feature of systemic diseases that may be life threatening and thus require proper diagnosis and treatment. Because of the wide spectrum of potential manifestations and the complexity of diagnostic methods, multidisciplinary collaboration is required to optimize patient management.

A bidirectional relationship has been suggested between periodontal inflammation and immunologically mediated conditions underlying DG. A recent systematic review underlined an increase in the incidence of periodontitis in patients with PV and MMP and worse periodontal conditions in DG-positive sites compared to the non-affected sites [3]. Despite

there is no evidence that DG *per se* can cause attachment loss and alveolar bone destruction [4,5], it may jeopardize patients' compliance in maintaining oral hygiene, which in turn may represent a risk for future periodontal health. Gingivitis and periodontitis have clinical features overlapping those of MMP or PV. Pathophysiological findings suggest further similarities between MMP and periodontitis. In both of the diseases the release of pro-inflammatory mediators (e.g. interleukin [IL]-6, IL-8, and matrix metalloproteinase [MMP]-1 and MMP-9) results in the destruction of structural component of the periodontium and in degradation of membrane basal zone components, respectively. Conversely, PV has different mechanisms of tissue injury but it still may promote periodontitis onset and/or progression when it occurs in form of DG by acting as a reservoir for plaque accumulation [6].

Finally, long-term corticosteroid therapy, which is usually required for diseases underlying DG, may have an effect on periodontal status as it alters the host immune response [7]. Thus, even treatment for OLP, PV and, in a minority of cases MMP, may have an impact on patients' periodontal status, especially if the corticosteroid administration is prolonged over time. Therefore, adequate knowledge of disorders associated with DG and proper clinical training to treat and support patients suffering from DG are mandatory in clinical practice. On the other hand, periodontitis may have an effect on autoimmune bullous diseases. Hajishengallis (2015) suggested that local inflammatory process exacerbated in periodontal lesions might trigger and sustain the autoimmune response increasing the severity of symptoms of the systemic condition [8].

The present article is intended to answer the following f*ocused question*: "What are the most relevant findings about the diagnosis and subsequent treatment of DG?". The available scientific literature will be reviewed in order to collect data about mucocutaneous diseases associated with DG and to provide proper guidelines for their clinical management with particular attention to the scientific findings of the last three years.

Epidemiology

The conditions more frequently associated to DG are MMP [9,10], OLP [11,12], and PV [6,13,14], with the first two accounting for 80% of cases, and PV together with other rare conditions for the remaining proportion [15]. Despite in recent years the cases labeled as idiopathic have been drastically reduced thank to the improvement in immunologic analyses, it is still difficult to estimate the relative contribution of other conditions in the overall occurrence of DG because single cases or case series have been usually reported, and epidemiologic studies are sparse. These include EM [16,17], LE [18,19], graft versus-host disease (GVHD) [20,21], chronic ulcerative stomatitis [22,23], plasma cell gingivitis (PCG) [24], linear immunoglobulin A disease [25-27], dermatitis herpetiformis [28,29], epidermolysis bullosa acquisita (EBA) [30], paraneoplastic forms [31-33] foreign body gingivitis [34], and psoriasis [35,36].

In the past, DG has also been associated with a small group of non-immunomediated disorders that include endocrine-related conditions [37]. However, there is little evidence to support the hypothesis of hormone imbalance in DG.

Diagnosis

The diagnosis of DG is based upon clinical examination, but laboratory, and histopathological procedures are required to differentiate DG-associated disorders that, in spite of the similar clinical appearance, have different management and prognosis [38].

Determination of the etiologic factors that cause DG is complicated and takes a long time. As summarized in Figure 1 the fist step of the diagnostic pathway is taking a detailed medical history. Demographic characteristics, general health conditions, onset and progression of any existing gingival lesion, symptoms, and drug intake should be investigated meticulously. Conditions associated with DG generally have a peak of incidence between the fourth and sixth decade of life with a predilection for females. In many cases gingival lesions represent the onset of the disorder or appear very early during its clinical course [39-41].

The second and third steps focus on a careful intra- and extra-oral examination to analyze location, morphology of the gingival lesions, any contact with dental materials and presence of similar lesions at other sites of the body. Gingival lesions often have a polymorphous clinical appearance [42] with DG existing alone or more frequently in combination with other lesion morphologies. Sometimes, DG represents the only long-term clinical feature and can mimic plaque-related gingival inflammation causing a delay in diagnosis. The definitive diagnosis is based on histopathological characteristics of the tissues obtained from the oral lesions, in addition to examination of serum autoantibodies using immunofluorescence. However, the presence of distinctive oral and/or skin lesions may represent sometimes a valuable aid in guiding the differential diagnosis [43].

OLP

OLP is a cytotoxic T cell-mediated chronic inflammatory disease of unknown etiology that causes mucosal tissue breakdown by inducing apoptosis of basal keratinocytes via tumor necrosis factor-alpha release. An association with hepatitis C has been reported [44].

Clinical features include keratosis, erosions, vesicles, bullae and ulcers. When erosive/ulcerative lesions involve the gingiva this manifests as DG [45]. Erosive lichen planus compromises over 70% of cases of DG [46]. The onset is typically in the third to seventh decades of life and with a slightly higher frequency among women.

The most commonly affected site is the buccal mucosa, but the borders and the dorsum of the tongue and the gingiva may also be affected. Exclusive gingival involvement is observed in 7% to 10% of the cases [42]. Oral lesions generally involve multiple oral sites, and they are typically bilateral and symmetrical. The presence of whitish-grey plaques, called Wickham striae, is the most recognized sign of the disease, although it is not pathognomonic for OLP [47]. When erosive/ulcerative OLP lesions are present, the Wickham striae can often be seen at the periphery of the lesions and may support a provisional clinical diagnosis.

It should be considered that some dental restorative materials (amalgam, composites, cobalt and gold) might cause lichen-like reactions that can mimic the clinical features of idiopathic

OLP [48]. Such reactions should be suspected when lesions are confined to areas adjacent to dental restorations and they resolve after material replacement.

The symptoms vary from slight discomfort to severe pain depending on the type and extent of lesions and may significantly affect the patient's quality of life.

Screening for extra-oral mucosal localization is imperative because patients with OLP can often present with genital and esophageal involvement.

While a biopsy is recommended to rule out other oral diseases, it is mandatory when erosive/ulcerative lesions are present [49]. The biopsy specimen should be harvested from oral lesions but not from the gingiva because the inflammatory infiltrate associated with concomitant gingivitis may alter the typical OLP histological features [50]. Direct immunofluorescence (DIF) testing is usually negative or typically reveals linear fibrinogen deposition along the epithelial basement membrane zone, extending into the papillary lamina propria in a 'shaggy' pattern. Additionally, deposition of immunoglobulin M (IgM), immunoglobulin G (IgG), immunoglobulin A (IgA), and complement component 3 (C3) on cytoid bodies at the basement membrane zone or papillary lamina propria may be detected. DIF is a key tool in differentiating lichenoid drug reactions [51]. Because there is no known antibody-mediated component in the pathogenesis of OLP, indirect immunofluorescence (IIF) is generally not indicated.

Patients should be regularly monitored since 1% of them may develop a squamous cells carcinoma [52].

MMP

MMP is a rare, vesiculo-bullous autoimmune inflammatory disease involving mucous membranes containing squamous stratified epithelium [53]. Patients with MMP have autoantibodies directed against various proteins of the basement membrane, resulting in the formation of subepithelial blisters, and in subsequent ulceration and scarring.

It presents most commonly in the elderly (60 to 80 years of age) with female predilection. The initiating factor of the autoimmune response is unknown, but sometimes it may be drug-

related (e.g. furosemide) [54].

The oral mucosa is the most commonly involved site, affecting 90% of patients, and DG is the most frequent oral presentation. The other affected sites in the oral cavity are the buccal mucosa and the palate. Gingival involvement typically presents as erythematous patches progressing to bullae that do quickly rupture leaving irregular-shaped erosions. Healing occurs slowly without scarring. Sometimes reticulated white plaques resembling Wickham striae can be observed.

Patients can report a history of blistering and often they complain pain, dysphagia and chronic soreness, particularly when eating acidic foods [53].

Extra-oral mucosal localization is a frequent finding with conjunctiva (64%) and the skin (24%) the most frequently involved, with poorer prognosis [55].

The diagnosis should be made on the clinical presentation combined with the results of microscopic evaluation and IF. A typical subepithelial clefting is seen histologically and a band positive for IgG, IgA, or C3 along the epithelial basement membrane is evident on DIF [38]. Because of potential ocular involvement resulting in blindness in the more severe cases, an ophthalmologic examination should always be organized.

PV

Pemphigus is a relatively rare, chronic, autoimmune, vesiculo-ulcerative disease characterized clinically by blisters and erosions on the mucosa and skin, and histologically by intraepithelial bullae. Patients with pemphigus develop autoantibodies directed against cell-adhesion molecules on the surface of the squamous epithelial cells, leading to acantholysis, blistering, and erosion [56]. PV is the most frequent form of pemphigus, accounting for 80% of the cases. Most patients are in their fourth and fifth decade of life, and the disease is equally common in men and women with predilection for adults of Mediterranean or Jewish ancestry [49].

The onset of the disease is insidious, oral lesions evolve slowly and sometimes it takes several months to make a correct diagnosis. Oral involvement is the first manifestation of the

disease in 50% to 90% of the patients and usually precedes skin manifestations by several months. Intraorally, blisters tend to develop in areas subjected to frictional forces, such as buccal and labial mucosa, gingiva, dorsum of the tongue, hard and soft palate. They are prone to rupture leaving painful ulcers and erosions that take a long time to heal. Patients complain severe pain and can barely drink or eat leading to severe weight loss.

Skin involvement typically occurs on the scalp, face, and upper trunk, and rarely on the legs. It presents with bullae and erosions that heal without scarring but leaving residual hyperpigmentation.

Definitive diagnosis is based on clinical features, histopathology, and immunological data [57]. The Nikolsky sign may help to confirm bullous lesion morphology producing the separation of the epithelium from the underlying connective tissue on normal-appearing gingiva [58]. Due to its high specificity (96%) it represents a useful test in the preliminary detection of PV [58].

A biopsy is mandatory to confirm the diagnosis. A staband-roll biopsy is recommended to collect an adequate specimen because the epithelium can easily be lost and a perilesional site, not directly involving the gingiva, should be preferred [59].

Histological examination shows the acantholysis characterized by intraepithelial cleavage with bulla formation, and DIF analysis shows the intercellular space deposition of IgG and C3 in the epithelial layer [60]. Usually, elevated titers of autoantibodies against desmoglein-3 molecules, reported with IIF and ELISA, correlate with earlier stages of disease and provide useful information in assessing disease activity.

PV has a high mortality rate causing fluid loss, nutritional deficiency, and secondary infection when left untreated.

Other Conditions

EBA: it is a chronic subepidermal blistering disease associated with autoimmunity to type VII collagen within anchoring fibril structures located at the dermoepidermal junction. Diagnosis

is confirmed by skin biopsy and DIF, showing linear disposition of IgG and complement proteins at the basal membrane.

Linear IgA bullous dermatosis (LBD): it is a subepidermal blistering disorder. Skin biopsy reports blistering just under the epidermis, with eosinophils and neutrophils being prominent within the inflammatory infiltrate. DIF reveals linear deposition of IgA along the basement membrane. However, it is sometimes difficult to distinguish different forms of immunobullous diseases clinically and histologically, and antibody findings may overlap.

EM: it is diagnosed clinically. In patients who have target lesions with a preceding or coexisting Herpes simplex virus (HSV) infection, the diagnosis can be made easily. In unclear cases, such as an atypical presentation or recurrent EM without documented HSV infection, biopsy may help rule out other diagnoses. Laboratory tests (e.g., HSV-1 and -2, IgM and IgG) may confirm a suspected history of HSV infection, but it is not required.
Skin biopsy findings vary depending on the clinical morphology and the duration of the lesions as well as the area of the lesion from which the specimen is obtained (i.e., the center portion or the outer zone). The early stage of the red macules and papules shows a perivascular mononuclear cell infiltrate. Biopsy of the edematous zone of the target lesion may show pronounced dermal edema histologically; necrotic keratinocytes or epidermal changes usually occur in the central portion of the target lesion.

Chronic GVHD: It is an immunity disorder that occurs after allogeneic hematopoietic-cell transplantation and often shares features of autoimmunity and immunodeficiency. Diagnosis is generally based on clinical signs and symptoms and may be confirmed by biopsy.

Treatment

The treatment of DG requires the cooperation among specialists to handle the underlying disease. Physicians, dermatologists and oral pathologists may be consulted and treatment strategies may be discussed and shared in order to provide the greatest benefit to the patients.

The therapeutic goal of the treatment of DG is to slow down disease progression and mitigate the symptoms in order to preserve patient's quality of life. Monitoring is generally recommended and treatment is indicated only in cases where the lesions and symptoms affect the patient's daily habits [38]. Each and every case of DG requires the setting up of an accurate plaque control as a first line of therapy but topical therapy may be implemented to the hygienic phase. According to the underlying disease specific topical medications should be administered in order to mitigate the symptoms of DG. In severe cases, systemic treatment of the pathologies that cause DG may be required under the supervision of an oral pathologist and/or a dermatologist.

Topical Therapies

The most widely used drugs for topical therapy are corticosteroids, commercially available as gel or spray. The choice of the correct formulation may help to improve their effectiveness taking into account that the application in the mouth is jeopardized by saliva, tongue and mastication.

Topical corticosteroids in the form of gel should be the first-line medical treatment and may be sufficient for some moderate or mild forms of DG, especially in cases related to OLP, complex aphthous ulcers, EM and GVHD. For other pathologies (i.e. immunobullous diseases) they can be an effective adjunct to systemic therapy [61**]. It is advisable to avoid mouthwash formulations in cases of localized lesions in order to reduce the occurrence of side effects, such as candidiasis. Corticosteroid inhalers can be of benefit for patients with oropharyngeal disease, however for more refractory lesions an intralesional administration has to be preferred.

Topical medications for DG containing topical calcineurin inhibitors are also available and may represent an alternative to corticosteroids [61**].

Systemic therapy

Topical therapy alone is sometimes insufficient to control disease activity. When patients continue to experience erosions and pain despite topical therapy, treatment with systemic therapy is indicated. However, there is no universally agreed second-line treatment in the use of systemic corticosteroids [44,45,62-67].

Systemic therapy should be matched with the presumed duration of the disease considering that reappearance of lesions occurs frequently during short-term tapering of corticosteroid administration [61**].

Systemic therapies vary according to the underlying disease. Due to the complexity of the drug management and the severity of possible adverse effects, it is mandatory to refer patients to physicians, dermatologists and oral pathologists for treatment. In the following paragraph we reported treatment strategies for the main diseases underlying DG.

OLP

The treatment of OLP begins with an effective but non-traumatic supragingival removal of bacterial plaque followed by subgingival debridement. Topical corticosteroids are the medication of choice for the majority of patients that still complain for discomfort after the hygienic phase. Gel formulations are to be preferred and used with a custom-made gingival tray [68]. A beclomethasone spray may be used in cases of patchy involvement of the gingiva [69]. A recent systematic review underlined the effectiveness of 0.025% to 0.05% clobetasol propionate but also of 0.1% tacrolimus and 1% pimecrolimus as secondary alternative in their topical formulation [70]. Systemic corticosteroids could be considered in a second phase of treatment when topical treatment is ineffective. Finally, it has recently been reported that the effects of local corticosteroids can be increased by the adjuncts of immunomodulators [71] or lower-level-laser therapy [72].

MMP

Oral lesions are typically indolent. Proper oral hygiene and the administration of topical corticosteroid may be sufficient to reduce patients' discomfort. Systemic corticosteroids, azathioprine, sulphapyridine or dapsone may be used as adjunctive therapy especially if other mucosal or skin sites are involved [69].

PV

In mild case of PV, limited to oral manifestations, topical corticosteroid therapy with 0.05% fluocinonide is recommended. Severe cases may be treated with clobetasol. Finally, adjuncts such as analgesic, anti-inflammatory and anti-infective drugs may provide additional benefits [73]. Early diagnosis and therapy are crucial to avoid the involvement of skin and other mucosal sites. Referring to a dermatologist is compulsory as PV is a life-threatening condition.

DG in PV is treated with local corticosteroid but PV itself requires adjunctive treatment. First-line therapy consists of topical and systemic corticosteroids at high dosage. They may be administered *per os* or in form of pulse therapy with discontinuous intravenous infusions of a high dose of medication (e.g. ≥ 250 mg/die of prednisone) along with immunosuppressive agents. The aim of pulse therapy is to achieve a faster response and stronger efficacy of corticosteroids reducing side effects and the need for long-term administration. Azathioprine, cyclosporine, cyclophosphamide and methotrexate are the "steroid-sparing" therapy added to the corticosteroid during supportive care in periods of disease inactivity [73].

Other conditions

EBA

As it is a rare condition, treatment guidelines are based on small case series. Acceptable results have been reported for systemic corticosteroids, immunosuppressant, dapsone, colchicine, and intravenous immunoglobulin [74].

LBD

Dapsone and sulphapyridine represent the first-line of therapy. The disease shows good response to treatment. Alternative treatments include prednisone, sulfamethoxypyridazine, colchicine, dicloxacillin, mycophenolate mofetil and intravenous immunoglobulin. In refractory cases it is possible to use a medium dose of steroid [60].

EM

Treatment with continuous antiviral drugs is the only therapy validated in the literature. Other treatments lack scientific evidence. The use of thalidomide, immunoglobulin and azathioprine relies on small case series [75]. Systemic corticosteroid therapy is recommended for Major EM [61**].

Chronic GVHD and chronic ulcerative stomatitis

They can be treated by topical corticosteroids in case of oral involvement. PCG requires the identification and removal of the underlying inciting agent [61**].

Periodontal treatment in DG patients

Although DG is not directly caused by dental plaque biofilm the severity of the clinical manifestations often depends on plaque accumulation and subsequent gingival inflammation [76]. Current evidence does not provide generally established guidelines for treatment of DG [38, 77*-79], however management must be comprehensive and include meticulous attention to oral hygiene in order to avoid *Candida* colonization and periodontal damage [80]. A high prevalence of periodontal pathogens was also found in DG lesions [81].

All patients with DG should have a thorough examination of the oral cavity. The clinician should carefully inspect gingiva and teeth for accumulation of dental plaque, signs of gingival retraction, evidence of caries, dental root exposure and tooth loss. All mucosal surfaces should be inspected for the presence of microbial colonization, including evaluation for the white plaques of oral candidiasis [61**].

Although different protocols have been proposed for plaque control, some general principles should be applied for all patients with DG. Current evidence shows that dental hygienists should deliver intensive plaque control programs during the initial phase of DG assessment, and check the patient adherence to a proper daily oral hygiene regimen during supportive periodontal therapy [61**,76,82]. The ability to achieve low plaque levels depends on patient's motivation that in turns depends on patient's comfort during home oral hygiene. Symptomatic ulcerative or erosive gingival involvements lead to painful oral lesions that can compromise effective plaque control [38]. The selection of adequate devices may be important to increase patient's compliance even in cases of symptomatic DG. Mild manifestations of DG usually include sensitivity to spicy and acidic food, or discomfort to some dentifrices, the most severe presentations have an impact on patient's quality of life and discourage patients to perform optimal plaque control [38,67].

As Stone and coworkers demonstrated, a personalized plaque control program is cost effective in managing gingival manifestations of DG [83]. Although this could not lead to a complete resolution, the use of a sonic toothbrush and extra-soft interdental brushes has been successful in reducing plaque and improving signs and symptoms of DG, with statistically significant differences regarding related symptoms, plaque index and mucosal disease score [76]. Sonic toothbrush generates high-amplitude and high-frequency bristle motion, creating a gentle dynamic cleaning action that drives fluid forces along the gum-line and is capable of dislodging dental plaque in hard-to-reach areas [84]. Brushing-induced turbulence has been shown to drive fluid dynamic forces at a distance of 3 mm between the dental surface resulting in an effective biofilm removal into the more inaccessible areas of the oral cavity and causing minor gingival abrasions than a manual toothbrush [85,86]. This is more relevant when managing with painful atrophic mucosa that may discourage patients from brushing effectively [38]. A recent study reported greater clinical benefit for an intensive plaque control program with sonic compared with manual toothbrush in patients with DG associated to OLP [87*]. Clinical scores and patient-related outcomes showed a significantly greater benefit in patients instructed to use a sonic toothbrush. A further report described a

larger decrease of gingival crevicular fluid volume and of MMP-1 and MMP-9 levels in the patients using the sonic toothbrush [88].

Other studies suggested the use of 0.12% chlorhexidine mouthwash as an adjunct to manual tooth brushing with or without the administration of corticosteroids in addition to professional plaque control and reported favorable clinical results [89,90]. The combined administration of topical corticosteroids and a motivation–behavioral skills protocol for oral hygiene has also been successfully applied to DG patients [91]. However, the additional administration of topical corticosteroids would seem to produce anti-plaque and anti-inflammatory benefits similar to those reported for the daily use of a sonic toothbrush [86,87*].

Conclusions

As DG is a non-plaque-induced inflammatory gingival lesion dental practitioners should consider it an oral manifestation of underlying systemic diseases. It is difficult for patients with DG to effectively brush their teeth because of pain, thus plaque accumulation may be an exacerbating factor of DG and may increase the long-term risk for development of plaque-induced periodontal diseases. Sonic toothbrushes have demonstrated an advantage compared to manual toothbrushes in terms of less patient discomfort during home care procedures. The painful symptoms and clinical features in gingiva are improved by meticulous oral hygiene procedures, but the underlying causes of DG cannot be eliminated by plaque control alone. Thus, cooperation with dermatologists/oral pathologists is always required to select the most appropriate topical or systemic treatment as adjunct to the institution of individually-tailored oral hygiene programs with minimal injury to the gingival tissue. Taking in consideration the prevalence of DG, it should be desirable to develop customized technologies for home care that may allow an improvement in the quality of life of patients with DG.

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Captions

Figure 1

Diagnostic pathways of the main mucocutaneous diseases associated with DG.

Table 1

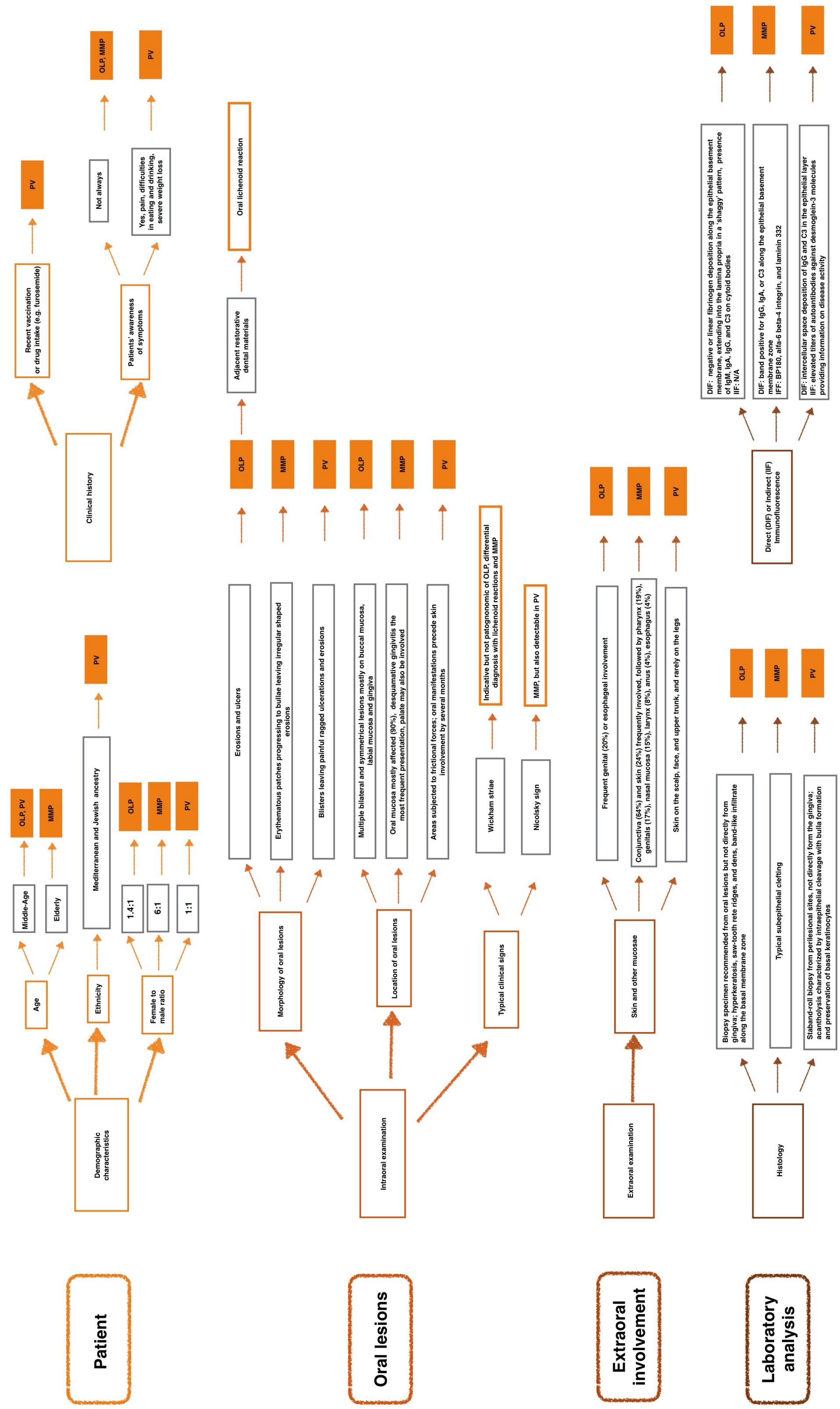
Conditions and diseases associated with non-plaque induced gingivitis.

Genetic/developmental disorders
- Hereditary gingival fibromatosis
Specific infections
- Bacterial origin
a.Neisseria gonhorrea
b. Treponema pallidum
c. Mycobacterium tubercolosis
d. Streptococcal gingivitis
- Viral origin
a. Coxsakie virus (hand-foot and mouth disease)
b. Herpes simplex I and II (primary or recurrent)

c. Varicella zoster (chicken pox & shingles – V nerve)
d. Molluscum contagiosus
e. Human papilloma virus (squamous cell papilloma, condyloma acuminatum, verruca vulgaris, focal epithelial displasia)
- Fungal origin
a. Candidosis
b. Other micosis
Inflammatory and immune conditions and lesions
- Hypersensitivity reactions
a. Contact allergy
b. Plasma cell gingivitis
c. Erythema multiforme
- Autoimmune diseases of skin and mucous membranes
a. Pemphigus vulgaris
b. Pemphigoid
c. Lichen plants
d. Lupus erythematosus
- Granulomatous inflammatory conditions (orofacial granulomatosis)
a. Crohn's disease
b. Sarcoidosis
Reactive processes
- Epulides
a. Fibrous espulis
b. Calcifying fibroblastic granuloma
c. Pyogenic granuloma (vascular epulis)
d. Peripheral giant cell granuloma (or central)
Neoplasm
- Premalignant
a. Leukoplakia
b. Erythroplakia

- *Malignant*
a. Squamous cell carcinoma
b. Leukemia
c. Lymphoma
Endocrine, nutritional and metabolic diseases
- *Vitamin deficiencies*
a. Vitamin C deficiency (scurvy)
Traumatic lesions
- *Physical/mechanical insults*
a. Frictional keratosis
b. Toothbrushing-induced gingival ulceration
c. Factitious injury (self-harm)
- *Chemical (toxic) insult*
a. Etching
b. Chlorhexidine
c. Acetylsalicylic acid
d. Cocaine
e. Hydrogen peroxide
f. Dentifrice detergents
g. Paraformaldehyde or calcium hydroxide
- *Thermal insults*
a. Burns of mucosa
Gingival pigmentation
a. Gingival pigmentation/melanoplakia
b. Smoker’s melanosis
c. Drug-induced pigmentation
d. Amalgam tattoo

Figure 1


Patient
Demographic characteristics
Age
Middle-Age
OLP, PV
Elderly
MMP
Ethnicity
Mediterranean and Jewish ancestry
PV
Female to male ratio
1.4:1
OLP
6:1
MMP
1:1
PV
Clinical history
Recent vaccination or drug intake (e.g. furosemide)
PV
Patients' awareness of symptoms
Not always
OLP, MMP
Yes, pain, difficulties in eating and drinking, severe weight loss
PV
Oral lesions
Intraoral examination
Morphology of oral lesions
Erosions and ulcers
OLP
Adjacent restorative dental materials
Oral lichenoid reaction
Erythematous patches progressing to bullae leaving irregular shaped erosions
MMP
Blisters leaving painful ragged ulcerations and erosions
PV
Location of oral lesions
Multiple bilateral and symmetrical lesions mostly on buccal mucosa, labial mucosa and gingiva
OLP
Oral mucosa mostly affected (90%), desquamative gingivitis the most frequent presentation, palate may also be involved
MMP
Areas subjected to frictional forces; oral manifestations precede skin involvement by several months
PV
Typical clinical signs
Wickham striae
Indicative but not patognonomic of OLP, differential diagnosis with lichenoid reactions and MMP
Nicolsky sign
MMP, but also detectable in PV
Extraoral involvement
Extraoral examination
Skin and other mucosae
Frequent genital (20%) or esophageal involvement
OLP
Conjunctiva (64%) and skin (24%) frequently involved, followed by pharynx (19%), genitals (17%), nasal mucosa (15%), larynx (8%), anus (4%), esophagus (4%)
MMP
Skin on the scalp, face, and upper trunk, and rarely on the legs
PV
Laboratory analysis
Histology
Biopsy specimen recommended from oral lesions but not directly from gingiva; hyperkeratosis, saw-tooth rete ridges, and dens, band-like infiltrate along the basal membrane zone
OLP
Typical subepithelial clefting
MMP
Staband-roll biopsy from perilesional sites, not directly form the gingiva; acantholysis characterized by intraepithelial cleavage with bulla formation and preservation of basal keratinocytes
PV
Direct (DIF) or Indirect (IIF) Immunofluorescence
DIF: negative or linear fibrinogen deposition along the epithelial basement membrane, extending into the lamina propria in a 'shaggy' pattern, presence of IgM, IgA, IgG, and C3 on cytoid bodies
IIF: N/A
OLP
DIF: band positive for IgG, IgA, or C3 along the epithelial basement membrane zone
IFF: BP180, alfa-6 beta-4 integrin, and laminin 332
MMP
DIF: intercellular space deposition of IgG and C3 in the epithelial layer
IIF: elevated titers of autoantibodies against desmoglein-3 molecules providing information on disease activity
PV