

COMMON ORAL MUCOSAL LESIONS

Author(s)

Maria Bankvall maria.bankvall@ki.se

Erik Dabelsteen erikdabelsteen@gmail.com

Palle Holmstrup pah@sund.ku.dk

Anne Christine Johannessen anne.johannessen@uib.no

Mats Jontell jontell@odontologi.gu.se

Evelyn Neppelberg, evelyn.neppelberg@odont.uib.no

Jaana Rautava jaana.rautava@helsinki.fi

Author(s)' title(s), degree(s), affiliation(s),:

Maria Bankvall, DDS/PhD, Department of Dental Medicine, Karolinska Institutet, Stockholm/Masthuggskliniken - Orofacialmedicinskt Centrum i Västra Götaland, Göteborg, Sweden

Erik Dabelsteen, DDS/PhD Professor emeritus, Odontologisk Institut, Det Sundhedsvidenskabelige Fakultet, Københavns Universitet, Danmark

Palle Holmstrup, DDS/PhD Professor emeritus, Odontologisk Institut, Det Sundhedsvidenskabelige Fakultet, Københavns Universitet, Danmark

Anne Christine Johannessen, DDS, MD, PhD, Professor emerita, The Gade Laboratory for Pathology, Department of Clinical Medicine, University of Bergen, Norway and Department of Pathology, Haukeland University Hospital, Bergen, Norway

Mats Jontell, DDS/PhD Professor emeritus, Department of Oral Medicine and Pathology, Institute of Odontology, Sahlgrenska Academy, University of Gothenburg, Sweden

Evelyn Neppelberg, DDS/PhD Associate professor, Department of Clinical Dentistry, Faculty of Medicine, University of Bergen, Norway and Head & Neck Division, Haukeland University Hospital, Bergen, Norway

Jaana Rautava, DDS/PhD Associate professor, HUS Head and Neck Center, Department of Oral and Maxillofacial Diseases, University Hospital Area, University of Helsinki, Finland

Corresponding author

Mats Jontell

Department of Oral Medicine and Pathology

Institute of Odontology

Sahlgrenska Academy

University of Gothenburg

PO Box 450

405 30 Göteborg

Sweden

SUMMARY

The rationale for choosing the lesions included in the present paper is that they are the most common oral mucosal diseases that general practitioners experience in their practice (Axell et al., 1976, Salonen et al., 1990, Robledo-Sierra et al., 2013). The key problem that general practitioners often encounter is to arrive at a correct diagnosis. Therefore, the primary goal of the present paper is to detail the clinical characteristics, as well as histopathological characteristics and other paraclinical examinations (when appropriate). Once a correct diagnosis is established, it is often possible to acquire information about appropriate management strategies through several different information sources. The paper and the presented lesions should be seen in perspective of paper IV of the present volume, where important differential diagnoses to the lesions in the present paper are portrayed.

Keywords: diagnosis, mouth disease, oral manifestations, oral mucosa, oral medicine, oral pathology

Headlines

- All general dental practitioners experience common oral mucosal diseases in their practice.
- Once a correct diagnosis of oral lesion is established, it is possible to acquire information about management strategies through different information sources.

CLINICAL RELEVANCE BOX

- All general dental practitioners experience common oral mucosal diseases in their practice.
- Once a correct diagnosis of oral lesion is established, it is possible to acquire information about management strategies through different information sources.

ANGULAR CHEILITIS

Angular cheilitis is primarily not a diagnostic problem since it has a unique location (Fig. 1). However, an increased understanding of the etiology and how the lesion is maintained is important for proper management (Blagec et al., 2022).

Clinical features

Older people with extended angular folds probably have equal potential to develop angular cheilitis regardless of whether they have dentures, but denture wearers specifically have a microflora that facilitates the development of the infection. Thus, the theory has been advocated that it is not the decrease in the vertical dimension *per se* that is of greatest importance but the presence of an extended of ageing tissue. Angular cheilitis in younger patients is characterized by a single rhagade limited to the corner of the mouth. Most of these patients report an atopic constitution and cutaneous disorders. (Blagec et al., 2022, Ohman et al., 1986).

Figure 1. Angular cheilitis



Aetiology and pathogenesis

The pathogenesis begins with a fissure at the corner of the mouth due to aging of the skin or atopy. The rhagade is then infected by fungi or *Staphylococcus aureus*. Older individuals are

usually infected by *Candida albicans*, while younger individuals more often contract the bacterial infection. (Blagec et al., 2022)

Treatment

The treatment is a combination of both antifungal and antibacterial drugs, such as miconazole. The drug may also be combined with hydrocortisone. It is important that the patient does not apply the drug with a finger since the risk of reinfection is high since *Staphylococcus aureus* can be found on the skin. Instead, cotton tops or other modes of application should be used. Once the infection has healed, it is important to keep the skin lubricated with a softening ointment to avoid relapses. Again, cotton tops or other modes of application are preferred, at least at the initial stages. (Cabras et al., 2019)

RECURRENT HERPES LABIALIS

Recurrent herpes labialis (RHL) is one of the most common human viral infections worldwide (Gopinath et al., 2023, Petti and Lodi, 2019).

Figure 2. Recurrent herpes labialis.



Clinical features

The most common location of RHL is the labial vermilion border (Fig. 2), appearing as cold sores, while intraoral infection is uncommon in otherwise healthy persons. The symptoms begin with a sensation of burning pain and itchiness and progress to a painful lesion. Herpetic vesicles manifest as clusters of small and often “thin-walled” microvesicles. These intraepithelial lesions may progress to pustules, erosions, and ulcerations and coalesce into larger irregular ulcers (diameter 0.5 - 1 cm) surrounded by an erythematous zone. Lesions eventually develop a crust and then resolve normally within 10 to 14 days and heal without scarring. (Arduino and Porter, 2008).

Aetiology and pathogenesis

RHL is caused by the reactivation of herpes simplex virus type 1 (HSV-1) in the trigeminal sensory ganglion. Primary HSV-1 infection is often mild, subclinical and asymptomatic. (Gopinath et al., 2023) However, the infection may lead to herpetic gingivostomatitis, fever and pain after an incubation of approximately 1 week (2-20 days after contact). In healthy persons, sunlight or ultraviolet (UV) light are well-known trigger factors for RHL. Other common trigger factors are fever, common cold and other viral infections, in addition to physical trauma, including dental treatment and physiological factors such as elevated levels of stress, dietary inadequacy, menstruation or hormonal shifts in women. (Petti and Lodi, 2019; Arduino and Porter, 2008)

Diagnosis

Diagnosis of RHL is usually based upon the clinical history together with presented features. HSV-1 serology is the gold standard through antibody detection. To confirm an HSV-1 infection, detection of viral DNA by direct PCR (polymerase chain reaction) assays is a highly sensitive method of identifying appropriately infected cells that are not dependent on viable virus. (Arduino and Porter, 2008). The sample procedure is simple, noninvasive and requires only standard media for bacterial or virus samples. A biopsy may be indicated if lesions are atypical and/or remain chronic without a normal healing pattern.

Treatment

Avoiding direct contact of affected lesions is important to reduce the risk of spreading the virus. For instance, washing hands is important, as is not sharing, for example, a toothbrush or a glass. Herpetic whitlow, also known as herpetic paronychia, presents as a local pain or burning sensation followed by deep blisters that may secondarily erode, affecting the distal phalanx of one or more fingers. (Petti and Lodi, 2019; Arduino and Porter, 2008) We mention it here as an occupational potential hazard for dentists to address the importance of using protective gloves during dental procedures. Ocular HSV infections may present with uni- or bilateral keratoconjunctivitis (Petti and Lodi, 2019; Arduino and Porter, 2008). Thus, dentists should wear protective glasses during patient procedures. Immunocompromised persons have a higher risk of RHL infection, longer duration of episodes, and are prone to comorbidities of HSV. For instance, viruses may spread to the central nervous system, causing encephalitis or meningitis (Petti and Lodi, 2019).

The list of early preventive or management interventions for people prone to RHL is long (Gopinath et al., 2023), including sunscreen or protection of lips (lip balms/moisturizers, zinc-based creams, aloe vera gel, ice cubes, etc.). In the early prodromal phase, antiviral therapy is recommended (not later than 48 hours in this phase), as the drugs act through virus-statics by

interrupting DNA replication. Numerous clinical trials conducted over the years still indicate that topical acyclovir 5% or penciclovir 1% remains the first-line therapy, being both effective and well tolerated (Gopinath et al., 2023; Petti and Lodi, 2019). Systemic antiviral agents such as acyclovir are recommended in more severe cases. In patients with severe pain, local anaesthetics or painkillers may be used to reduce symptoms. Topical corticosteroids for the treatment of RHL lesions are contraindicated, as virus infection may progress and spread into the tissue and cause delayed healing.

APHTHOUS STOMATITIS

This oral mucosal condition can be divided into recurrent aphthous ulcers (RAS) and aphthous-like ulcerations (ALU) depending on whether the ulceration has a presumed etiology. RAS is an inflammatory condition of unknown aetiology characterized by painful, recurrent, single, or multiple ulcerations of mainly the nonkeratinized oral mucosa in otherwise healthy individuals (Graykowski et al., 1966). These lesions often present in people aged 10-40 years, and a hereditary component may be present (Natah et al., 2004).

Figure 3. Aphthous ulcer on lip mucosa.



ALU, on the other hand, is an inflammatory condition characterized by painful, recurrent, single, or multiple ulcerations of mainly the nonkeratinized oral mucosa in patients with an underlying systemic disease, allergy, hematinic deficiency, or medication (Baccaglioni et al., 2011). Clinically, these lesions cannot be distinguished from RAS; however, they often run a more complex clinical course requiring more extensive medical screening and management (Cui et al., 2016).

Clinical features

Aphthous ulcers present as well-demarcated round or ovoid lesions with a necrotic centre covered by a yellowish or greyish-white pseudomembrane encompassed by an erythematous halo, with the surrounding regions left clinically unaffected (Fig. 3). It is not possible to look at the lesions to distinguish RAS from ALU. Ulcers of this kind are most commonly found on the labial and buccal surfaces. They may also present in the soft palate, ventral parts of the tongue, and floor of the mouth. They are rarely found on keratinized surfaces of the mouth, such as the gingiva, hard palate, or dorsum of the tongue. In addition, they are uncommonly found further down in the tonsils, uvula, and oropharynx, although when they are present in these areas, they are highly debilitating for the patient and more difficult to treat. (Natah et al., 2004)

Patients with RAS are classically afebrile, without pallor, concomitant genital or ocular ulcerations and present with no history of immunodeficiency, whereas patients with ALU may display these features. The lesions can vary in size from 1 mm to over 10 mm in diameter, present as single or multiple lesions and heal within one week up to several weeks, sometimes with scarring.

Aetiology and pathogenesis

Most likely, the aetiology behind RAS is multifactorial, where many different factors contribute to the lesions that are typical of this condition (Cui et al., 2016). Most patients are young and healthy but may have a hereditary component (Miller et al., 1980). However, aphthous ulcerations can be associated with other factors, such as systemic diseases, medications, hematinic deficiencies and hypersensitivity to certain food substances (Scully et al., 2008). Other factors that may influence aphthous ulcers are cessation of smoking, local trauma, dysbiosis of the oral microbiota, stress, salivary composition, toothpastes containing sodium lauryl sulfate (SLS) and hormonal changes (Akintoye et al., 2014).

Diagnosis

The diagnosis of RAS is mostly based on patient history, clinical examination and the exclusion of any underlying medical conditions or other contributory factors. There are currently no clinical diagnostic tests specific for RAS (Jurge et al., 2006). A biopsy is usually not necessary, as histopathological findings are not diagnostic and reveal only nonspecific ulceration. Sampling for viral, bacterial, or fungal infections can be required occasionally for differential diagnostic purposes. In the suspicion of ALU, a comprehensive medical history and clinical examination may guide the clinician through to a correct diagnosis. The most common systemic diseases include inflammatory bowel diseases, celiac disease, and Behcet's syndrome.

Any extraoral complaint should be thoroughly evaluated, and if needed, a referral to the general practitioner or appropriate specialist should be considered. It is important to ask patients about any regular pattern of recurrence and accompanying fever. Other site involvement, such as skin, genital or gastrointestinal, can be ascertained through a formal systems enquiry. Laboratory investigations are useful to help exclude a potential systemic cause.

Treatment

At present, there is no cure for RAS. Instead, all the available treatment strategies are aimed primarily at relieving symptoms, such as pain, and secondarily with a focus on promoting healing and reducing the inflammation and risk of secondary infection. While various topical and systemic therapies have been used to treat RAS, there are few publications demonstrating the efficacies of the different substances applied, as stated in a recent meta-analysis (Liu et al., 2022). Currently, there is no consensus available regarding appropriate treatment regimens for adults, and knowledge on the treatment of children barely exists (Liu et al., 2022).

Most patients have limited symptoms and do not require treatment. However, for those patients who do have symptoms, implying difficulties of eating and speaking, there are several options based on the simplest measure in relation to side effects and costs.

Pharmacological treatment:

- Topical analgesics (for example benzydamine hydrochloride)
- Systemic analgesics (for example, paracetamol, ibuprofen and naproxen)
- Topical steroids (for example Triamcinolone and Clobetasol propionate)
- Systemic steroids (for example, prednisolone)
- Topical antibiotics (for example, chlortetracycline)
- Other systemic treatments (for example, colchicine, pentoxifylline, dapsone, thalidomide, levamisole, montelukast, clofazimine and various biological therapies)

NORDIC SNUS-ASSOCIATED ORAL LESIONS

In Nordic countries, snus primarily exists in four different forms: moist lose-weight snus (LWS), moist snus in pouches (SP), tobacco- and nicotine-free snus in pouches (TNfS) and

tobacco-free nicotine pouches (NP). Oral mucosal lesions related to the first three forms show a similar appearance.

Clinical features

The lesions are graded using four different stages according to the degree of severity (Axell et al., 1976). The period of use and type of snus correlate to the degree of severity. The wrinkling and thickness of the oral mucosa (Fig. 4) increased in the following order: LWS/SP/TNfS. Gingival retractions have been observed in as many as 18% of the study individuals (Kopperud et al., 2023). In the majority of cases, a completely normal mucous membrane is observed within a few weeks following cessation of snuff use. The cancer risk from snuff is extremely low, and epidemiological studies have not established causality. However, it cannot be completely ruled out that one or a few isolated cases may exist, probably in individuals who have used loose snuff for a long time (Hirsch et al., 2012). One must keep in mind that snuff other than Nordic snus, such as American or Asian snuff, bear a very different risk for cancer.

Figure 4. Snus-associated lesion.



Since its introduction in 2016, nicotine-free snus in pouches (TNfS) has become increasingly popular. In a recent study (Alizadehgharib et al., 2012), 60 Swedish smokeless tobacco users were encouraged to substitute their snus with nontobacco-based nicotine pouch products during a 6-week period. Over time, a reduction in preexisting oral mucosal lesions was observed between baseline and the final visit. Although the scientific knowledge of oral mucosal lesions associated with TNfS is very limited, an increase in the number of reported cases to SOMnet, a Swedish national electronic network for oral medicine, has been seen. These lesions are different from traditional oral mucosal lesions and have a more lichenoid nature. However, a more scientific evaluation is needed to ensure its existence.

Diagnosis

The topical relation to the pouch and the disease history led to the diagnosis.

ORAL LEUKOPLAKIA

It is well known that carcinoma of the oral mucosa is sometimes preceded by a whitish or reddish lesion. This is why such lesions have been identified as potential precursors of cancer, now often termed ‘oral potentially malignant disorders’ (OPMDs), previously usually denoted premalignant lesions (PL), which we consider a more correct term. In fact, most patients diagnosed with PL do not develop oral carcinoma, but the lesions are associated with an increased susceptibility to cancer development (Warnakulasuriya et al., 2021). The most important PLs in Scandinavia are leukoplakia and erythroplakia, the latter being extremely rare.

Clinical features

Leukoplakia can involve any site of the oral mucosa and may be uni- or multifocal and show a range of clinical features (Warnakulasuriya, 2020). Homogeneous leukoplakia is characterized by a whitish, sometimes corrugated surface (Fig. 5), while nonhomogeneous leukoplakia shows a surface with white or red areas, often with nodules or seldom with verrucous excrescences. Leukoplakia has been described with a prevalence of 1% to 5% (Axell, 1976, Napier et al., 2008, Petti, 2003).

Figure 5. Oral leukoplakia.



Aetiology and pathogenesis

Although it has been the intention for a couple of decades to exclude lesions caused by tobacco from the diagnosis of leukoplakia, several problems are associated with this practice. First, it is

difficult to quit smoking and thereby explore the causal role of tobacco. Second, in smokers, the etiological role of tobacco is unknown. Third, in many countries, including those in the Far East, a causal role of various smoking habits for leukoplakia has been regarded as a factor. Furthermore, virus ((Nielsen et al., 1996, Sundberg et al., 2019) and yeast infection (Krogh et al., 1987) have been suggested to be involved in the etiology of leukoplakia. Thus, Candida infection has been described in as many as 27-81% of cases (Rindum et al., 1994). However, there is no doubt that some oral leukoplakias have an unknown cause (Napier and Speight, 2008). A study in private dental practice in the UK showed that heavy smokers were more likely to have leukoplakia or oral lichen planus by a factor of 3.58 for females and 3.68 for males (Lim et al., 2003). This study also showed that heavily drinking men were approximately three times more likely to have such a lesion and that the prevalence increased with long-term use of tobacco and alcohol. In addition, a study carried out among the Bangladeshi population of East London showed a prevalence of leukoplakia of as high as 25%, with a positive association with betel quid chewing (Pearson et al., 2001).

Studies of early stages of cancer development have resulted in the theory that cancer arises in areas with cellular genetic alterations associated with malignancy. Such so-called precancerous fields according to the theory of field cancerization may remain invisible up to the point of malignant progression in patients with *de novo* tumors. However, a precancerous field may also manifest itself as a visible lesion, such as leukoplakia. (Braakhuis et al., 2003; Califano et al., 1996; Partridge et al., 2000; Pindborg et al., 1968; Poell et al., 2023). The invisible changes in the border zones of leukoplakia may explain why surgical removal of the lesions appears to have a low success rate (Holmstrup et al., 2006).

Diagnosis

The patient's history and clinical examination as well as a biopsy should exclude other known diseases. Among lesions that do not fulfil the diagnosis of leukoplakia are affections that are reversible after elimination of traumatic influences on the mucosa, e.g., masticatory friction, friction from exaggerated use of a toothbrush and/or a sharp tooth that hits the tongue during chewing.

Treatment

The basic concept of handling oral leukoplakia is to prevent malignant transformation, but currently, no universally approved therapy regimen has been established to distinguish which lesions will transform into a carcinoma (Holmstrup and Dabelsteen, 2016). As mentioned above, the reduction of tobacco consumption is important but a difficult task for patients. Surgical removal of the lesions has been shown not to eliminate malignant development, which is why patients should be continuously followed independently of surgical removal. However, since unrevealed carcinomas have been identified after serial sections of surgically removed lesions, excision may be recommended for diagnostic purposes. It may be advisable to refer patients with high-risk leukoplakia to specialist clinics for diagnostic investigation and follow-up (Holmstrup, 2009). In addition, it is important to note that nonhomogenous leukoplakias are frequently infected by *Candida* species and, if so, should be treated with antimycotics, which may result in changes in clinical appearance (Krogh et al., 1987).

Prognosis

Between 0.3 and 17.5% of oral leukoplakia cases may be associated with the development of oral cancer (Pindborg et al., 1968; Holmstrup et al., 2016; Chaturvedi et al., 2020; Reibel, 2003). However, some leukoplakias may remain unchanged throughout the patient's lifetime, and others even disappear spontaneously (Holmstrup et al., 2006). A significant reduction in

tobacco consumption has resulted in a decrease in size or the disappearance of many lesions (Roed-Petersen, 1982). In general, nonhomogeneous leukoplakias carry a higher risk of malignant transformation than homogeneous leukoplakias (Holmstrup et al., 2006; Lind, 1987; Speight et al., 2018). A long-term follow-up study showed a seven times increased risk for nonhomogenous types compared with homogenous types and a 5.4 times increased risk for lesions exceeding 200 mm² (Holmstrup et al., 2006; Evren et al., 2020). While the risk of malignant transformation of OL in some studies has been related to the location (Kramer et al., 1978), other studies have not found site-associated differences in the risk of future malignant development (Holmstrup et al., 2006; Silverman et al., 1984).

The histological demonstration of epithelial dysplasia in a biopsy in several studies appears to be related to an increased risk of malignant development (47-51)(Kramer et al., 1978; Silverman et al., 1984; Cowan et al., 2001; Lumerman et al., 1995; Pindborg et al., 1977), yet other studies have questioned such a relationship (Holmstrup et al., 2006; Brouns et al., 2014; Fonseca-Silva et al., 2016), and it is remarkable that 40% of cancers arise from biopsied leukoplakia without dysplasia. Part of the explanation may be that biopsies of leukoplakias may not be representative of the most advanced dysplastic changes in the lesion or that cellular genetic alterations may not be envisioned as dysplastic changes in all cases (Chaturvedi et al., 2020; Holmstrup et al., 2007; Thomson et al., 2002). Taken together, the finding of epithelial dysplasia should be regarded as a sign of concern, but the lack of epithelial dysplasia is no guarantee of a course without risk of malignant development.

LICHENOID DISORDERS

Lichenoid disorders comprise several clinical and histologically similar affections of the oral mucosa, including lichen planus, which is an inflammatory disease of skin and mucosa, lichenoid contact lesions, e.g., in relation to dental fillings, lichenoid drug reactions, and graft-

versus-host disease. It has been proposed that rather than distinguishing between several conditions, the collective term "oral lichenoid disease" should be used until further knowledge is established (Warnakulasuriya et al., 2021).

Clinical features

The characteristic clinical picture of lichenoid disorders is the appearance of whitish streaks and papules (Fig. 6), often on a reddish background, but more uncharacteristic lesions, such as diffuse atrophic, reddish or whitish plaque-like changes, are usual, and sometimes ulcers appear (Thorn et al., 1988). If untreated, it is common for the lesions to persist for many years, but some lesions may change their clinical appearance. Thus, after many years, plaque-type lesions often appear, and sometimes it is difficult to distinguish such lesions from leukoplakia, especially since the typical lichen changes often disappear with time (Thorn et al., 1988).

Figure 6. Lichenoid lesion on buccal mucosa.



The lichenoid contact lesions are limited to the area of contact with the triggering dental material and therefore are usually unilateral as opposed to the other types of lichenoid lesions (Bolewska et al., 1990). Oral lichenoid reactions in graft-versus-host disease (GVHD) are a complication that occur in recipients of allogeneic hematopoietic stem cells or bone marrow.

The WHO has characterized oral lichen planus and oral lichenoid reactions as potentially malignant conditions (8)(Arduino et al., 2019). In patients with oral lichen planus, an increased development of oral cancer, i.e., on the order of 0.5-1.5%, has been observed in Denmark and Sweden (Holmstrup et al., 1988; Rodstrom et al., 2004).

Aetiology and pathogenesis

The etiology of lichen planus is not established, and neither is any predisposing factor. Each of the other categories of lichenoid lesions are associated with an identified causal factor, e.g., treatment with filling materials for contact lesions (Bolewska et al., 1990), treatment with drugs for drug reactions and receipt of allogeneic hematopoietic stem cells or bone marrow for GVHD-associated lesions.

A striking histopathologic feature of oral lichenoid disorders is the subepithelial band-shaped inflammatory infiltrate dominated by lymphocytes characteristic of a type 4 hypersensitivity reaction, which also causes degenerative changes in the epithelial basal layer (Holmstrup and Soborg, 1977).

Diagnosis

Lichenoid contact reactions, drug-induced lichenoid reactions and the clinical manifestations of GVHD bear a striking resemblance to oral lichen planus both clinically and histopathologically. The diagnosis of drug-induced lichenoid reactions requires that a temporal connection can be demonstrated for the onset of the lesions and the administration of the suspected drug (e.g., antineoplastic and immunomodulating drugs) and whether the change disappears when the drug is discontinued. The clinical manifestations of GVHD alone are often sufficiently diagnostic, provided they are present in a patient who has received allogeneic hematopoietic stem cell transplantation. (Al-Heshimi et al., 2007)

Treatment

In the case of symptoms linked to atrophic and ulcerating gingival lesions, it is important to carry out gentle but effective oral hygiene, which usually requires careful instruction of the patients. It is important not to brush directly on the soft tissue, as traumatic impact can worsen the lesions (Holmstrup et al., 1990). Secondary Candida infection of the lesions is common, and antimycotic treatment may sometimes resolve pain-giving ulcerous lesions. In cases of symptomatic lichenoid lesions on the inside of the upper lip in need of additional treatment, anti-inflammatory and anti-infectious therapy can be added, e.g., chlorhexidine 0.12–0.20% (Backman and Jontell, 2007). If necessary, it can be supplemented with antifungal treatment and topical steroid treatment. The treatment of contact reactions consists of replacing the

triggering dental material, e.g., amalgam or composite, with, for example, gold or ceramics. GVHD usually requires systemic immunosuppressive treatment, including treatment with high-dose oral corticosteroids (Baumrin et al., 2022). Patients should be followed by a regular dentist and only referred to a specialist dentist if there are special problems, including if malignancy is suspected (Mattsson et al., 2002).

GEOGRAPHIC TONGUE (GT)

Clinical features

The diagnosis of geographic tongue (GT) is primarily clinical, so it is fundamental to be acquainted with its clinical appearance. GT has several designations, such as benign migratory glossitis and erythema migrans. As the name suggests, this oral mucosal lesion is localized to the tongue but can also be found in other parts of the oral mucosa and is then called geographic stomatitis. GT is characterized by multiple well-defined areas that have a depapillated erythema in the centre often surrounded by a slightly raised yellow–white border in the periphery. (Picciani et al., 2017). The multiple lesions can sometimes form larger areas, giving the impression of a geographical appearance (Fig. 7). GT can disappear and reappear for periods of days, weeks, and months. In some cases, the GT lesion transforms into a fissured tongue. A recent meta-analysis

Figure 7. Geographic tongue.



of GT arrived at both the period prevalence and the point prevalence of 3.0% in the general population (Pereira et al., 2022).

Most patients affected by GT do not report any discomfort. However, some patients complain of soreness, increased tongue sensitivity and burning sensations usually elicited by the intake of acidic foods and drinks.

Aetiology and pathogenesis

The etiology of GT remains largely unknown, but psychosomatic and hereditary factors have been proposed to have a role in the etiology of this mucosal lesion (Alikhani et al., 2014).

Diagnosis

GT rarely causes any major diagnostic problem. In certain cases, however, the clinical picture may differ, which justifies a biopsy. Inflammation characterizes the histology of the red depapillated areas of GT with loss of keratin and present with neutrophil, lymphocyte and plasma cell infiltrates and intraepithelial microabscesses. (McNamara et al., 2019)

Treatment

Unfortunately, there is no well-established treatment for patients suffering from GT (Gonzalez-Alvarez et al., 2018). However, it is good to advise patients to reduce the intake of spicy, salty and acidic food, treat parafunctional habits, reduce stress levels, use products for dry mouth when necessary, eliminate the use of tongue scrapers or use local products such as lidocaine, xylocaine or benzydamin.

PIGMENTED LESIONS

Diagnosis of pigmented lesions of the oral cavity can be challenging. Clinical evaluation and assessment of differential diagnoses of the lesions should take into consideration the wide range of colours, from brown, black, grey, or blue, and the variation in number and extension. In addition, there may be overlapping clinical characteristics. (68-72)(Dhanuthai et al., 2022; Lambertini et al., 2018; Meleti et al., 2008; Rosebush et al., 2019; Tavares et al., 2021). In general, a detailed clinical examination and medical history are important for the diagnosis.

Clinical features and etiology

A systematic overview of the various types of pigmentations is presented in Table 1. Clinically, pigmented lesions may present as focal (solitary), diffusely spread or as multiple oral and perioral spots. There may be clinical overlap between the different categories. (Dhanuthai et al., 2022; Meleti et al., 2008, Tavares et al., 2021)

Oral pigmentation may be physiologic, such as ethnic pigmentation. Such pigmentation is mostly diagnosed clinically. They manifest as diffuse or patchy symmetric brown pigmentations, most often in the gingiva. On the other hand, pigmentation may be the result of a pathologic condition, which requires a more careful analysis of the clinical picture.

Pigmentations can either be caused by melanin (located in melanocytes in the basal epithelial layer of the oral mucosa) or be nonmelanotic. The nonmelanotic group is rather diversified and includes exogenous pigmentations, such as amalgam tattoos, heavy metal pigmentations, or medicament-induced pigmentations. The exogenous pigmentations are most often gray or black and reflect metal depositions in the mucosa, such as silver or heavy metals such as arsenic, bismuth, lead and mercury. (Rosebush et al., 2019)

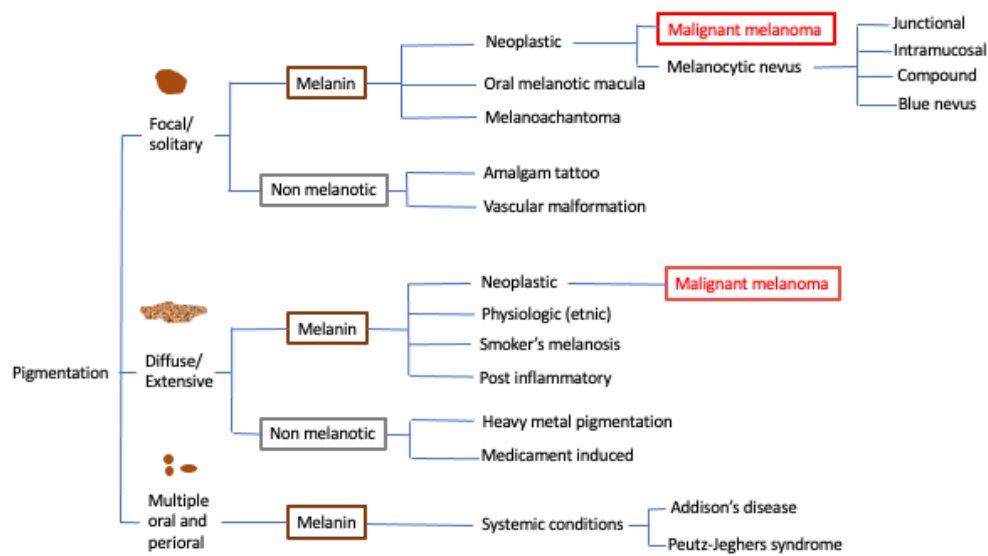


Table 1. A schematic overview of the various types of pigmentations.

Figure 8. Melanotic macule.



The most common pigmented lesions of the oral mucosa have been reported to be *amalgam tattoo*, *oral melanotic macula* and *melanocytic nevus* (Dhanuthai et al., 2022; Tavares et al., 2021). *Amalgam tattoo* (focal argyrosis) manifests as gray or blue macules as a result of traumatic implantation of amalgam during dental treatment. They are stable over time and in most cases without symptoms, since the foreign bodies are well tolerated by the body, provided they are implanted as small granules. Most often, they are located close to the teeth, preferably in the gingiva, but if, by accident, larger pieces of amalgam have been implanted in regions at a certain distance from the teeth, the diagnosis may not be obvious. In such cases, a foreign body reaction may have occurred, and lesions can be more extended.

The oral melanotic macule is a solitary homogeneous brown-to-black macule and is often <1 cm in diameter (Fig. 8). The macules are most often located in the gingiva and at the vermilion border, but they may occur at any location of the oral mucosa. Labial lesions are almost exclusively located on the lower lip. The pigmentation can be explained by increased production and deposition of melanin in the basal cell layer of the epithelium and in melanophages in the connective tissue. (Dhanuthai et al., 2022; Tavares et al., 2021)

Intraoral melanocytic nevus may present as a macule or as an elevated papule or nodule <0.5 cm. It is most often located in the palate and less common in the buccal mucosa, labial mucosa, gingiva, alveolar ridge, and vermilion border. It is a benign tumor containing nevus cells. Histologically, four different subtypes are recognized (Table 1), depending on the location of the nevus cells. The most common type is intramucosal nevus, followed by blue nevus. (Dhanuthai et al., 2022; Tavares et al., 2021) There is no indication that an intraoral melanocytic nevus may undergo malignant transformation (Lambertini et al., 2018).

Diagnosis

Solitary pigmented lesions of the oral mucosa may mimic an early stage of malignant melanoma, which is extremely rare in the oral mucosa. Rapidly growing pigmented lesions should always be biopsied. Location in the palate increases the rate of suspicion of malignant melanoma. In skin, the ABCD checklist (asymmetry, border, irregularities, colour variation, and diameter > 6 mm) can be used in the diagnosis of cutaneous malignant melanoma. Such a checklist may also be used in the clinical diagnosis of oral melanoma. Histopathological diagnosis of pigmented lesions is important since there is an overlap in the clinical appearance of benign pigmented lesions and malignant melanoma. (Meleti et al., 2008) Therefore, when in doubt, a biopsy must be performed to reveal the accurate diagnosis of this group of lesions (Dhanuthai et al., 2022; Lambertini et al., 2018).

PEMPHIGUS VULGARIS

Clinical features

Pemphigus vulgaris is an autoimmune bullous disease that typically involves the oral mucosa and skin. Due to autoantibodies against adhesion molecules on the surface of the epithelial cell lining of these tissues, intraepithelial bullae or erosions are formed (Fig. 9). Primarily due to secondary infections, the mortality rate is nearly 100% at the end of 5 years if left untreated.

Although several effective treatment modalities are available, there may still be a 2-fold increase in the death rate compared with the general population. (Alpsoy et al., 2015).

Figure 9. Pemphigus vulgaris



Pemphigus vulgaris occurs most frequently when patients are 50 to 60 years old, with an overall incidence that is slightly higher in females. Incidence estimates vary around the world according to geographic area and ethnic groups (Alpsoy et al., 2015; Kasperkiewicz et al., 2017). The annual pemphigus incidence reported in northern Europe (Finland and Germany) is 0.5-0.98 per million, and in Iran, it is 16 per million, whereas the reported incidence for Israel and a Jewish population in the USA is 50 and 32 cases per million population, respectively (Kasperkiewicz et al., 2017; Hietanen and Salo, 1982). With increased immigration to Northern Europe, it is likely that the incidence of pemphigus vulgaris will increase in Scandinavia.

In nearly half of the patients, oral mucosal lesions develop before the skin lesions. Bullae that occur in the mouth are fragile and easily break, leaving irregular erosions, which

are initially red but may later be ulcerated and covered by fibrin. Skin lesions usually appear 2-3 months later. (Kasperkiewicz et al., 2017; Pollmann et al., 2018)

Aetiology and pathogenesis

It was a breakthrough for the understanding of the disease mechanism and treatment possibilities when it was demonstrated that patients had antibodies to the epithelial cell membranes and that the amount of these antibodies correlated with disease activity. Later, it was shown that these antibodies are autoantibodies against the proteins desmoglein 1 and 3, which are adhesion molecules on the surface of epithelial cells. In most patients with disease localized to mucous membranes, only desmoglein 3 antibodies are found, whereas patients with mucocutaneous disease have antibodies against both desmoglein 1 and 3. These autoantibodies cause disease by the breakdown of cell adhesion. (Hammers and Stanley, 2016) Genetic factors have been identified as risk factors, although the correlation is unclear (Kasperkiewicz et al., 2017). In some patients, environmental factors seem to play a role. For example, drugs such as penicillamine and captopril may interfere with the epithelium or the immune system and trigger an outbreak of pemphigus vulgaris (Korman et al., 1991).

Diagnosis

Histopathologically, pemphigus is characterized by lost adhesion of the epithelial cells in mucosa and skin, which is why the epithelium separates just above the basal epithelial cell layer, leaving the remaining epithelium as a single cell layer covering the connective tissue, clinically appearing as an erythematous lesion, denoted an erosion (Fig. 9). The diagnosis is based on clinical, histopathological, and immune pathological findings, often leaning on laboratory techniques from blood samples. (Hammers et al., 2016; Murrell et al., 2020)

Pemphigus vulgaris should be suspected in any patient with mucocutaneous erosions or bullae; histologically detected supra basal splitting of epithelium strongly supports this diagnosis, which may be further supported by demonstrating antibodies to epithelial cell membranes and/or to desmoglein. (Hammers et al., 2016; Kershenovich et al., 2014; Murrell et al., 2020)

Treatment

Physicians, usually dermatologists, take care of patients with pemphigus. Systemic corticosteroids administered at high daily doses have dramatically improved the prognosis, reducing mortality to < 10%. However, after prolonged use, this is associated with significant side effects. Corticosteroid-sparing agents have been introduced to reduce the total dose of systemic corticosteroids. Other immunology-based treatment strategies have been introduced in recent years. (Pollmann et al., 2018; Scully and Challacombe, 2002) Oral lesions may improve by minimizing irritations and by careful oral hygiene (Scully and Challacombe, 2002).

MUCOUS MEMBRANE PEMPHIGOID

Mucous membrane pemphigoid (MMP) is a group of diseases characterized by bullous eruptions or ulcerations primarily at mucous membranes and concurrent autoantibodies to antigens in the basement membrane zone. MMP is a clinical phenotype in which subepithelial bullous formations may be induced by autoantibodies. It is a heterogeneous group of disorders with a chronic course and is primarily a disease of the mucous membranes, but occasionally the skin is involved as well. Previously, other names have been used to describe these conditions, including cicatricial pemphigoid, benign mucous membrane pemphigoid, oral pemphigoid, desquamative gingivitis, ocular cicatricial pemphigoid, and anti-laminin-5 cicatricial

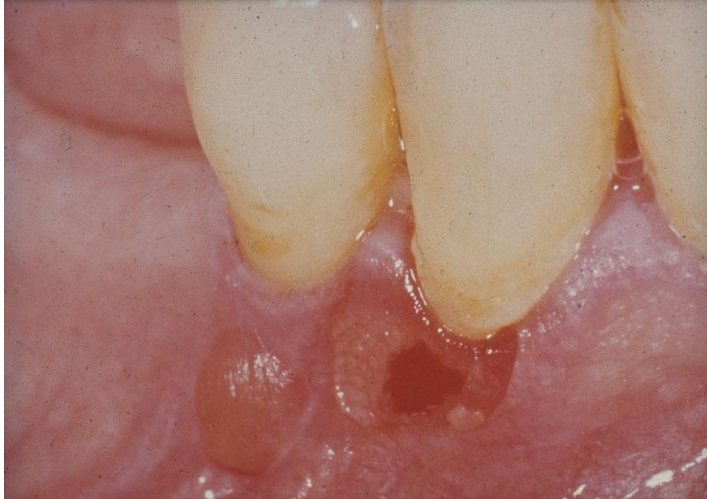
pemphigoid. Because it is difficult to clinically distinguish the various subgroups, the collective term mucous membrane pemphigoid is now accepted. (Chan et al., 2002; Lever, 1953)

Clinical features

The incidence of MMP is estimated at approximately 1.3 to 2.0 per million people. It characteristically presents in the 6th decade of life, and the female-to-male ratio is approximately 2-1. (Bernard et al., 1995). MMP most frequently affects the oral mucosa, but in 50% of patients, other mucous membranes (ocular, nasopharyngeal, laryngeal, esophageal, and genital) are also involved. Cutaneous involvement is usually absent or limited. The disease is severe with a varying prognosis, and healing of affections may produce irreversible scarring, except in the oral cavity. Thus, ocular affection may result in scarring with abnormal adhesion of the bulbar and palpebral conjunctiva (symblepharon), which may result in blindness. (Chan et al., 2002, Murrell et al., 2012)

In the oral mucosa tense, sometimes hemorrhagic bullae develop; however, they often break due to trauma from normal functions, leaving ulcers covered by fibrin (Fig. 10). The lesions that may resemble late pemphigus lesions heal slowly. On attached gingiva, lesions may appear as diffuse reddening, often described as desquamative gingivitis. When lesions are biopsied, there is a tendency of the epithelium of the surrounding mucosa to loosen due to impaired adhesion of the epithelium to the underlying connective tissue. (Schmidt et al., 2013)

Figure 10. Bullae of mucous membrane pemphigoid.



Aetiology and pathogenesis

There is clinical and experimental evidence that autoantibodies to basement membrane proteins play a central role in the pathogenesis of the disease (Chan et al., 2002). MMP autoantibodies may target different antigens in the basement membrane zone, and long-term follow-up studies indicate that the extent and severity of oral disease often correlate with antibody levels in patient serum (Chan et al., 2002; Rashid et al., 2006). Genetics, including HLA alleles, which are a complex of genes encoding cell-surface proteins responsible for the regulation of the immune system, have been identified as risk factors (Hesari et al., 2023). It has been debated whether a minority of MMP patients have an increased relative risk of cancer; however, recent findings show that the rate of cancer in MMP patients does not differ from that of the general population (Chan et al., 2002).

Diagnosis

The diagnosis of MMP is based on clinical findings and detection of basement membrane zone autoantibodies. Basement membrane-bound antibodies can be identified by immunofluorescence staining of tissue sections from biopsies of lesions or surrounding mucosa, and other immunological techniques can detect circulating antibodies (Bernard et al., 2013).

When repeated immunological investigations are negative, the diagnosis of MMP cannot be supported. (Murrell et al., 2012; Rashid et al., 2006; Schmidt et al., 2021). Histopathologic features may be helpful but not conclusive; they are characterized by separation of the epithelium from the connective tissue at the level of the basement membrane zone (Schmidt et al., 2021).

Treatment

Due to the possible severe prognosis of extraoral MMP affections, it is important that the dentist pays attention to systemic manifestations when seeing patients with bullous lesions. Appropriate treatment and monitoring of MMP thus require a multidisciplinary team involving dermatology, dentistry, ophthalmology, and otorhinolaryngology. Topical corticosteroids are recommended as first-line therapy in mild/moderate oral MMP and as adjunctive therapy in moderate to severe oral MMP. (Buonavoglia et al., 2019) For gingival lesions, careful gentle oral hygiene often has a substantial positive effect by reducing the inflammatory burden of the periodontal tissues depending on the clinical distribution of lesions (Lee et al., 1991).

FIBROEPITHELIAL HYPERPLASIA

Fibroepithelial hyperplasia is a reactive condition named after the clinical and histopathological presentation. It consists of fibroepithelial overgrowth because of injury or local irritation and is not a neoplasm. There is often an additional inflammatory component.

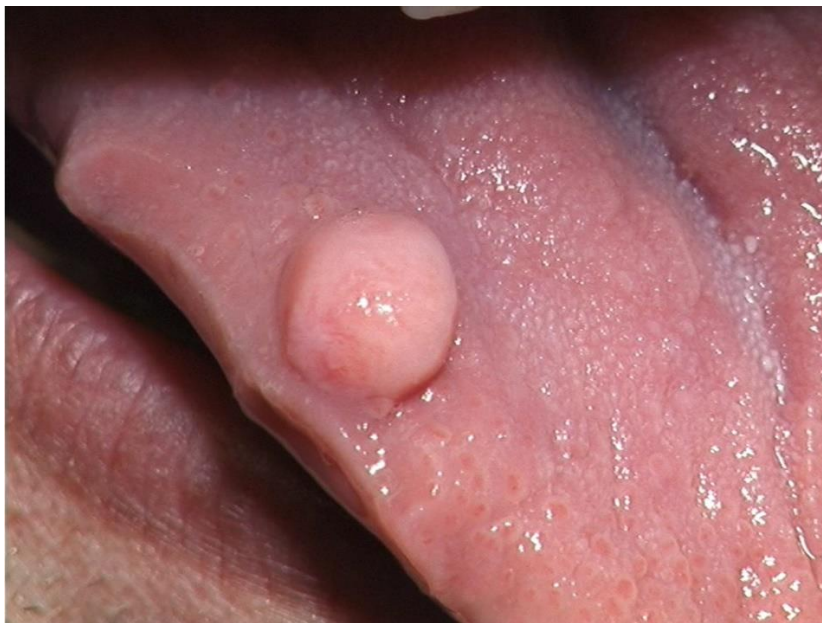
Clinical features

Etiological factors consist of trauma or irritation, such as biting, fractured tooth, poor plaque control with calculus formation, local foreign body, or ill-fitting dentures. These factors cause

mucosal irritation with a proliferative tissue response, often with some inflammation. (Dutra et al., 2019, Lakkam et al., 2020)

Clinically, these present as local, nodular growth (Fig. 11). The size is variable, but often they are rather small, less than 2 cm. They arise anywhere in the oral mucosa but most often on the buccal and lip mucosa as well as the gingiva and mobile tongue. They occur at any age but most often in 20-40-year-old adults with a female predominance. Fibroepithelial hyperplasia is often asymptomatic but may provoke discomfort or alter oral function, such as mastication or speech. They may also possess esthetic problems. (Dutra et al., 2019, Lakkam et al., 2020)

Figure 11. Fibroepithelial hyperplasia on tongue.



Aetiology and pathogenesis

Recurrence is uncommon and is mostly caused by repetitive trauma at the same site.

Diagnosis

Fibroepithelial hyperplasia is a diagnostic challenge. It may mimic various pathologic processes, rarely even malignant lesions. (Brierley et al., 2019, Vasanthi et al., 2022) The excision of the lesion is the choice of treatment, and there is a need for histopathological analysis to confirm the clinical diagnosis (Vasanthi et al., 2022). Histology shows fibroepithelial hyperplasia often with diffuse and mild lymphoplasmacytic inflammatory infiltration. The epithelium is parakeratinized and without dysplastic phenomena.

Treatment

Treatment is excision by surgery using local anaesthesia. Management should also always include the removal of irritative factors such as fixing the fractured tooth or ill-fitting prostheses or in case of poor hygiene and/or calculus, professional cleaning, and education of oral hygiene. (Brierley et al., 2019, Vasanthi et al., 2022)

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