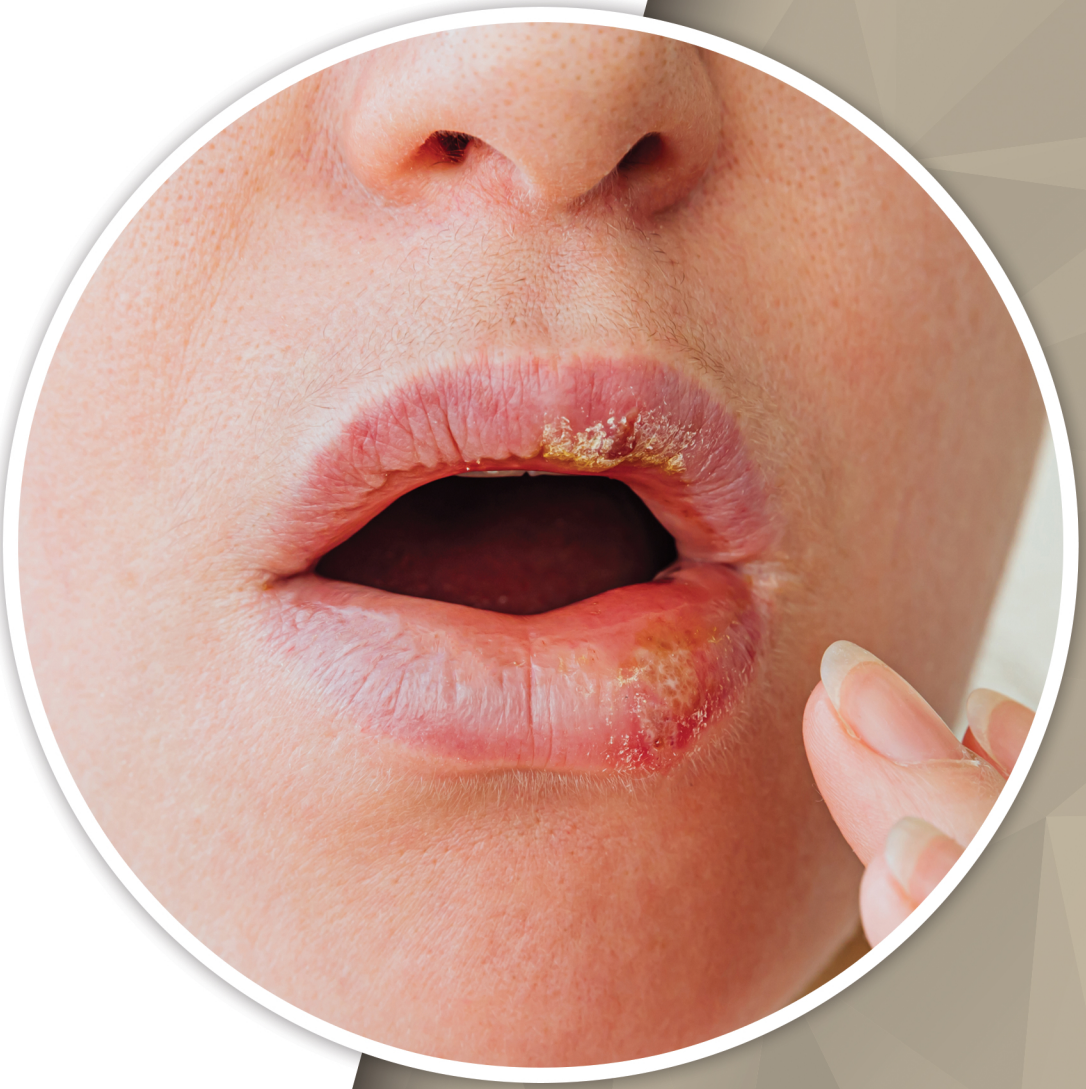
COMMON LIP DISEASES

A CLINICAL GUIDE



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Common Lip Diseases: A Clinical Guide

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PREFACE

Oral pathology is a specialized medical branch that is continuously evolving, thanks to the expansion of current knowledge and increasing clinical experience.

Progressive patient care in oral medicine requires a thorough knowledge of many disciplines of medicine and dentistry. Similarly, other related medical branches benefit from their understanding and insight into overall patient management. Therefore, a key aspect of this branch is that it bridges the gap between dentistry and medicine. For this reason, the authors have chosen the lip as the anatomical district of interest because, even today, there is no clarity on the relevance of the specialized medical figure. Often, patients do not know that it pertains to the oral cavity; therefore, the dentists specializing in oral pathology and often dermatologists, not being specialized in this anatomical field, do not have great expertise in these pathologies that also have manifestations in the mucous membranes of the oral cavity.

Therefore, the primary objective of this atlas is to provide the reader with a very didactic text that is easy to read and a quick reference that aims to update the most common pathologies of the oral cavity with lip manifestation.

Furthermore, the importance of the diagnosis of some pathologies, including actinic cheilitis, was underlined, due to the risk of neoplastic evolution. In the text, some lip manifestations of systemic immunological diseases have been extensively discussed, including lichen planus, erythema multiforme, pemphigus vulgaris, and vitiligo, which, if not diagnosed, can have very serious outcomes.

Finally, the last chapter is a brief overview of our outpatient clinical practice, based on the treatment of the most common lip diseases by phototherapy and photodynamic therapy (PDT), which are widely chosen by patients for their advantages over other surgical and pharmacological ablative therapies. We trust you will enjoy reading and using this little atlas as much as we enjoyed writing it.

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CHAPTER 1

Infectious and Inflammatory Cheilitis

Abstract: A broad spectrum of infections can occur in the oral cavity. These can be classified according to the etiological agent in bacteria, viruses and fungi. The most common bacterial infections are more putative in the hard tissues of the teeth, the pulp organ and periodontal tissues. Fungal infections are caused by opportunistic fungi that are generally present in the oral microbiota. In the oral and perioral regions, they are mainly attributed to Candida albicans. As far as viral infections are concerned, the oral and perioral cavity can be infected with numerous viruses, each capable of determining a rather distinct clinical-pathological picture. Herpes viruses are the most common and, in most cases, cause local disease in the short term. Human papillomaviruses are responsible for clinically distinct, rosy-white, exophytic verruca-papillary lesions with a typical surface alteration that gives a granular or cauliflower appearance.

Keywords: Candida albicans, HPV, HSV-1, Herpes labialis, Oral candidosis, Verruco-papillary lesions.

INTRODUCTION

Patients with oral viral infections are a common finding in outpatient clinical practice. Both primary and secondary or recurrent injuries can be extremely painful and debilitating, especially in patients with systemic diseases. The most common of the viral lesions is herpes simplex virus (HSV) infection. Secondly, oral lesions associated with the human papillomavirus stand out. HPV-associated oral lesions include verruca vulgaris, focal epithelial hyperplasia, and condyloma acuminate. Bacterial infections of the oral cavity can be divided into non-odontogenic and odontogenic. The most common odontogenic infections are caries, gingivitis, periodontitis, endodontic infections, dental abscesses and pericoronitis. Bacteria present in dental plaque are the most common cause of odontogenic infections. Oral candidiasis is the most commonly encountered superficial oral fungal infection. In fact, about 70% -80% of fungal infections are caused by Candida albicans, a fungus normally present in the flora of the digestive and vaginal tract of humans. Other Candida species, such as C. glabrata and C. tropicalis, represent approximately 5% and 8% of those reported. Therefore, this chapter focuses on the infectious pathologies of the labial mucosa

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most frequently encountered in outpatient clinical practice: herpetic and HPV-related viral infections and Candida albicans fungal infections.

Herpes Simplex Infections

Primary Herpetic Gingivostomatitis

Herpes simplex type 1 (HSV-1) and type 2 (HSV-2) represent a group of nine double-stranded DNA herpesvirus (HSV) species belonging to the *Herpesviridae* family [1]. The first type mainly infects the orofacial region, and the second type infects the genital area. HSV-1 is globally endemic, but recent studies in the literature report that it is becoming more common than HSV-2 as a cause of genital mucosal infections in young women [2, 3].

Primary oral HSV-1 infection is characterized by a productive infection and lytic activity directed against epithelial cells and limited to the viral entry site. The resulting local inflammatory process, possibly enhanced by bacterial co-infections, leads to the development of primary herpetic gingivostomatitis after an incubation ranging from 2 to 20 days [4]. A vesicular rash develops on the affected area, the vesicles of which very quickly result in very painful confluent ulcers. The typical red color is due to the hypervascularization of the underlying connective tissue that occurs as a result of inflammation, while pain is related to the loss of integrity of the epithelial barrier with consequent exposure of the underlying sensory nerve endings [4]. Initial lesions gradually increase in diameter, favoring the formation of coalescing central ulcerations due to the exposure of the lamina propria and underlying connective tissue [5]. The ulcerations are covered with yellow-gray pseudomembranes. Adjacent lesions can fuse to form irregular ulcerations [5]. Primary herpetic gingivostomatitis is often accompanied by local lymphadenopathy. The lesions can appear on the skin, vermilion and oral mucosa. Intra-oral lesions can affect the palatal, lingual, gingival mucosa and, less frequently, the pharyngeal (with pharyngotonsillitis) and nasal (with rhinitis) mucosa (Fig. **1**) [5, 6]. Clinically, there is widespread gingival edema. Ulcers gradually heal in about 10-14 days in the absence of scarring [7, 8]. Perioral lesions occur in three-quarters of patients with primary herpetic gingivostomatitis affecting the lips, cheeks and chin [7]. Occasionally, ocular (ocular herpes or herpetic keratoconjunctivitis) and digital (herpetic whitlow) infections may also occur [9]. The development of primary herpetic gingivostomatitis is often preceded by generic, non-pathognomonic signs and symptoms, such as fever, chills, nausea, loss of appetite, lethargy, irritability, general malaise, and headache. Sometimes, prodromal symptoms are the only signs of primary HSV-1 infection, and sometimes, they can be so mild (or even absent) that those affected do not remember it [4]. Older adults who develop

primary herpetic gingivostomatitis usually show mild lesions and an absence of lymphadenopathy. In contrast, primary herpetic gingivostomatitis among young adults is statistically more severe [10]. Primary herpetic gingivostomatitis is generally mild or asymptomatic since productive infection (*i.e.*, viral replication) and lytic activity are minimal [4]. Peaks in incidence occur during childhood (between 5 and 6 years) and adolescence in developing countries, whereas in rich nations, the incidence is more frequent in adulthood (between 20 and 40 years) [11]. Less frequently, clinically severe forms of primary herpetic gingivostomatitis may occur, in which purpuric macular rashes and arthralgia are present. Intraoral symptoms include dysphagia and odynophagia, which may be severe enough to require hospitalization [12].

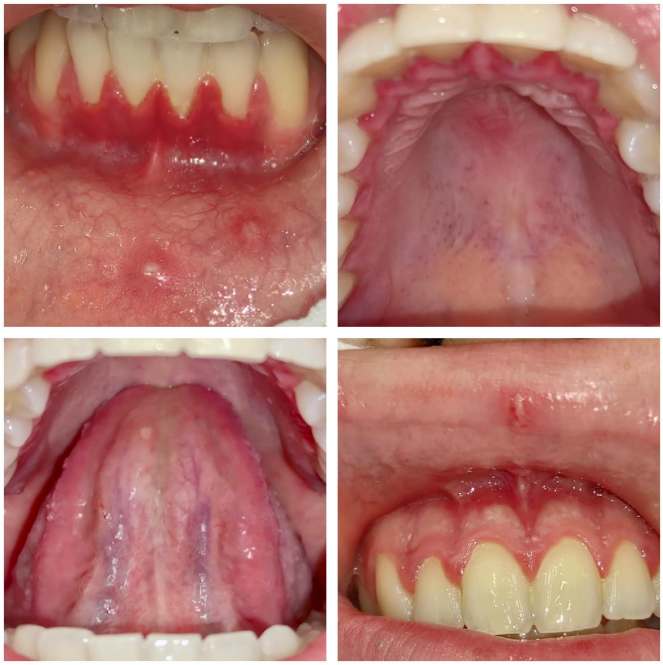

Fig. (1). Herpetic lesions in the vesicular phase involving all the intraoral mucous membranes in a young patient.

Herpes Labialis

Herpes labialis is the most common recurrence in immunocompetent individuals. Recurring extra-oral herpes can affect any site along the sensory area innervated by the trigeminal nerve, including the skin of the nasal pyramid, chin, or cheek, although the vermilion and mucocutaneous lip junction is the most commonly involved [13]. The first clinical symptom is a vesicular rash. Subsequently, these vesicles give rise to irregularly shaped coalescing ulcers (Figs. **2** and **3**). After

CHAPTER 2

Labial Traumatic Diseases

Abstract: The oral tissues, for obvious anatomical reasons, are exposed to continuous mechanical and inflammatory traumatic insults. Both reactive and pure traumatic hyperplastic injuries have been dealt with in this chapter. Reactive hyperplastic lesions are tumor-like hyperplasias caused by a tumor-like non-neoplastic proliferation due to chronic irritative stimuli. The most common reactive lesions include morsicatio labiorum, buccarum and traumatic fibroma. Among the purely traumatic ones, hematoma, ecchymosis and mucocele (affecting the minor salivary glands) stand out. These lesions can be generalized to large areas of the mucous membrane of the oral cavity or localized as solitary neoformations. Furthermore, according to the clinical aspect, they can be divided into plain (*e.g.*, keratosis), exophytic (*e.g.*, mucocele and fibroma) and endophytic (*e.g.*, traumatic ulcers). Reactive traumatic injuries often present diagnostic challenges because they mimic other pathologies of a non-traumatic nature.

Keywords: Ecchymosis, Fibroma, Hematoma, Morsicatio, Mucocele, Reactive hyperplasic lesions.

INTRODUCTION

This chapter focuses on traumatic lesions of the labial mucosa caused by chronic trauma and sudden trauma.

Among the former, the most popular ones in outpatient clinical practice are traumatic fibroma and morsicatio labiorum. These are the result of chronic low-intensity irritation that stimulates an exuberant tissue repair response. Particularly, the overproduction of collagen is the predominant basic aspect of the microscopic picture. Fibroblasts are mature and widely distributed in a dense collagen matrix. The overlying epithelium is often hyperkeratotic due to chronic low-intensity trauma. Basically, traumas can be classified according to etiology into two large

groups: mechanical trauma (bruises, abrasions and grazes) and thermal trauma (burns, caustics and freezing). Bruises are lesions of the skin due to a direct trauma that does not cause discontinuity of the epidermis, although deeper layers

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can be damaged. Abrasions are lesions due to a smear trauma, creating a discontinuity of the surface skin. Grazes are lesions due to a smear trauma, creating a discontinuity of the entire skin.

The latter include mucocele, ecchymosis and hematoma.

Mucocele or mucous extravasation cyst is caused by the rupture (due to a traumatic event) of the glandular excretory duct. Lips are the most affected site in absolute because they are the ones most exposed to trauma and because they have a high number of minor salivary glands located inside the internal labial mucosa superficially. The bleeding of the oral mucous tissues is the result of damage to the blood vessels, which consequently causes blood extravasation. They are usually caused by compressive trauma.

Morsicatio Labiorum and Buccarum

Morsicatio buccarum is a pathological self-induced condition caused by a chronic irritative stimulus, including the habit of sucking or modifying the oral mucosa [1 - 6]. When the site involved is the labial vermilion, it is called morsicatio labiorum (Fig. **1**) [4, 7]. This injury is associated with anxiety conditions, stress and mental illness [1, 7, 8]. The clinical symptoms of morsicatio labiorum are multiple lesions with a white-gray color that can undergo bacterial or fungal inflammation [1, 9]. The most frequent lesions are arranged transversely along the lines of occlusion and can also appear as plaques or nodular lesions soft on palpation called “buccal diapneusias” [10]. The differential diagnosis includes all white lesions of the oral cavity, including lichen planus, candidiasis, pemphigus or pemphigoid, linea alba, leukoedema, white nevus, and chemical burns [2 - 4, 7, 11, 12]. An aid in diagnosis is the correspondence of the lesions with the teeth, which can direct the clinician toward an etiological traumatic factor [3]. The diagnosis is clinical, especially when the habit of sucking or biting the lips is confirmed by the patient. In the literature, a recent study suggests that dermoscopy may be useful in differential diagnosis [13]. However, in most cases, patients are not aware of this habit, and in these cases, an incisional biopsy may be recommended in order to rule out other conditions. Psychological supportive therapies and the use of dental devices are recommended to prevent this condition [3].

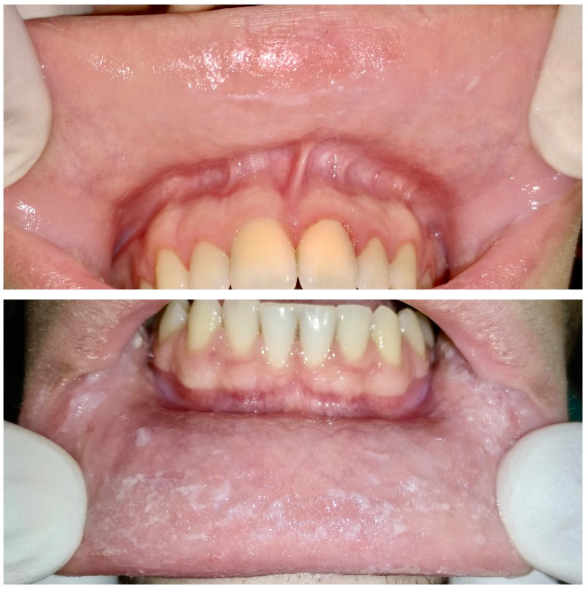

Fig. (1). Morsicatio labiorum of the internal labial mucosa, prevalent in the lower one. The patient confirmed the habit of biting her lips and the inner lining of the cheek during the day.

Mucocele

Mucocele is a lesion characterized by the retention of mucus [14 - 22]. From an etiological and histopathological point of view, it is possible to make a distinction based on the cause of the mucoceles. In fact, they occur following trauma or obstruction of the minor salivary gland. In the former case, they are called "extravasation cysts" and in the latter, "retention cysts" [23]. The most common is the former, which represents about 80% of mucoceles [24, 25]. They represent the most common pathology associated with the minor salivary glands and are the second benign lesion in order of frequency among the soft tissue neoformations of the oral cavity after traumatic fibroma [26]. In fact, a recent retrospective study pointed out that mucocele is the most frequently diagnosed lesion in all age groups [27, 28], especially during childhood [29 - 35]. The clinical manifestation is a rounded and circumscribed swelling of the mucosa, surrounded by the epithelium or covered by granulation tissue that is transparent or bluish in color, of variable size, fluctuating and soft on palpation (Figs. **2** and **3**) [36]. For anatomical reasons, the lower lip is the most affected [37 - 41]; however, mucoceles have also been documented in the upper lip [17] and other oral sites [42 - 46]. History and physical examination are the crucial points in the diagnostic process, thanks to the easy accessibility and inspection of the lesions. In particular cases, diagnosis may require the aid of first and second-level diagnostic techniques such as radiography, ultrasound, computed tomography (CT), and

CHAPTER 3

Labial Immunological Diseases

Abstract: Autoimmune diseases are caused by autoantibodies targeting structural proteins present in the skin and mucosa. The oral mucosa is frequently affected in these diseases, in particular by lichen planus, recurrent aphthous stomatitis, erythema multiforme, Stevens-Johnson syndrome and pemphigus. Clinical symptoms are heterogeneous and may present clinically with erythema, erosions and ulcers localized on the oral mucosa, causing a plethora of local and systemic symptoms, including pain, dysphagia, difficulty in eating and speaking and general malaise. The multiplicity and similarity of the clinical manifestations of these pathologies make an accurate diagnosis based only on the clinic extremely difficult. Therefore, to make a correct differential diagnosis, the clinic must be accompanied by a histopathological examination. The management of oral lesions accompanied by painful symptoms is challenging and requires a multidisciplinary approach. The main purpose of treatment is usually directed at reducing the pain and discomfort caused, controlling the worsening of the disease, and preventing complications.

Keywords: Allergic labial disease, Aphthous stomatitis, Erythema multiforme, Exfoliative cheilitis, Immune-mediated diseases, Lichen planus, Lupus erythematosus, Pemphigus vulgaris, Vitiligo.

INTRODUCTION

Immune-mediated pathologies of the oral cavity and, consequently, of the lips have very variable clinical aspects that make their diagnosis very complex. These conditions often remain unrecognized and are even confused with fungal or viral infections or malignant neoplasms. An aspect that should not be underestimated is that some immune-mediated diseases involving the oral cavity can also affect the skin and other mucous membranes. Often, the oral cavity represents the first manifestation of these immune-mediated pathologies. For this reason, dentists play an important role in diagnosing these conditions. They can, therefore, reflect the oral manifestations of dermatological and systemic conditions. As far as pathogenesis is concerned, immune-mediated diseases are pathological conditions that occur when the immune system is activated against components of the organism itself. The most common immune-mediated skin diseases discussed in this chapter are lichen planus, aphthous stomatitis, exfoliative cheilitis, erythema

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multiforme, Melkersson-Rosenthal Syndrome, lip vitiligo, and Crohn's disease. Among the immune-mediated pathologies, we have included those on an allergic basis: angioedema and atopic labial dermatitis.

Lichen Planus

Lichen planus (LP) is a chronic inflammatory disease involving skin and mucous membranes. The cutaneous lichen planus is more frequently detectable by the flexor surfaces of the extremities. It manifests clinically in the form of small, itchy, violaceous papules whose size can vary from a few millimeters up to becoming large coalescent plaques. As for the involvement of the mucous membranes, the oral cavity is often the only place of manifestation, however, the genital, laryngeal, esophageal and conjunctival mucous membranes may also be involved [1]. The exact incidence and prevalence of LP are unknown; in fact, data is heterogeneous within different geographic regions, with rates reported between 0.1 and 4% [2]. Oral lichen planus (OLP) occurs more in women than men, on average, around the fourth decade of life, although both children and the elderly may be affected [3]. The pathogenesis is a cell-mediated autoimmune type; the antigenic modification of basal epithelial cells triggers an autoimmune response mediated by T lymphocytes, which attack the keratinocytes of the basal layer recognized as non-self. Most of the T cells present in the OLP are represented by CD8 + cytotoxic T lymphocytes, which are able to determine the death of basal keratinocytes, triggering apoptosis through a pathway mediated by TNF-alpha. In the inflammatory infiltrate, however, we also find non-cytotoxic T-helper lymphocytes that play an important role in the pathogenesis of OLP. In fact, it has been suggested that CD8 + T lymphocytes and antigenic receptors present on CD4 + T lymphocytes bind to a specific antigen present at the level of class 1 and 2 MHC complexes present on basal keratinocytes. This binding causes Th1 CD4 + lymphocytes to release cytokines (IL-2; IFN-gamma), which stimulates CD8 + T lymphocytes to initiate lysis of target cells [1]. Contrary to the cutaneous area, in the oral cavity, the disease assumes a very heterogeneous clinical aspect attributable to distinct forms that have been described in the literature [4]:

-**Reticular**, the most common manifestation, is characterized by the peculiar "*Wickham striae*": an intertwining of keratotic white lines typically located bilaterally on the genetic mucosa;

-**Papular**, in which there are small papules of about 0.5 mm diameter, is rarely found due to the absence of symptoms;

-**Atrophic or erythematous**, characterized by erythematous areas furrowed by thin keratotic striae, is often associated with the erosive form;

-**Erosive**, in which there are painful eroded areas, is peripherally surrounded by erythematous areas and thin, finely radiating keratotic striae;

-**Plaque-like**, characterized by homogeneous whitish flat or raised areas similar to leukoplasic lesions; the back of the tongue and the buccal mucosa are the main areas affected;

-**Bullous**, a more unusual clinical form, whose vesicles of varying sizes result in extremely painful erosions in a very short period of time. This form occurs mainly at the level of the buccal mucosa at the lower molars [5]. When localized in the gingival area, it requires a differential diagnosis to distinguish it from other bullous diseases including pemphigus and pemphigoid.

The erosive, atrophic and bullous forms are more characterized by a reduction in the quality-of-life style of affected patients due to the strong impact on social relationships, psychological state and daily activities [6]. Furthermore, in a recent review of the literature, M. Giuliano *et al*. showed a neoplastic evolution rate of OLP of 1.40%. Erosive forms, female gender and lingual site have been identified as additional risk factors [7]. In the specific case of labial lichen planus (LLP), some cases are described in the literature [8 - 12]. According to a recent Italian review of the literature on LLP, the lower lip is the most affected site, mainly located on the inner edge of the lower vermilion (Figs. **1**-**4**) [10]. Furthermore, the erosive forms (28.57%) did not show a clear predominance (lower/upper lip ratio 6:5) [10]. These results were confirmed by another very recent review [10]. Diagnosis is mainly clinical, especially when classic bilateral *Wickham striae* are present. However, confirmation is always histological. Due to the absence of a known etiological factor, the chronic course of this pathology, and often the associated symptoms, the therapeutic approach is mainly aimed at controlling pain, which is particularly present in the case of atrophic-erosive lesions, in order to improve the patient quality of life. The most widely administered therapy, in patients for whom the need for a pharmacological approach has been established, is represented by corticosteroid drugs, systemically or topically administered [13]. However, the long-term use of steroids, especially systemically, can lead to the onset of adverse effects such as candidiasis [14], requiring antifungal therapy with consequent burning sensation, dysgeusia and inhibition of the hypothalamus-pituitary-adrenal axis [15]. Other pharmacological therapies are then described (calcineurin inhibitors [16], retinoids [17], methotrexate [18, 19], bevacizumab [20]), along with relevant adverse effects [21 - 26]. Recently, numerous laser therapies have been applied for the treatment of oral lichen planus, with good results and no side effects [27 - 32].

CHAPTER 4

Labial Manifestations of Systemic Diseases

Abstract: The oral cavity reflects the general health of the organism. Signs of a systemic or syndromic pathology often appear first in the oral cavity rather than systemically. Systemic diseases that can cause oral manifestations include endocrinopathies, oncological, cardiovascular, gastrointestinal and neurological diseases. Oral lesions caused by the treatment of systemic diseases can also be clinically significant, including those caused by cancer therapies (mucositis) and drugs that alter salivary flow. Some clinically observable changes in the oral cavity are disease-specific, while others may simply increase the dentist's level of suspicion. This short chapter deals with some important systemic pathologies with labial manifestation: Crohn's disease, Melkersson-Rosenthal syndrome, and chemotherapy-induced mucositis in cancer patients.

Keywords: Chemotherapy-induced mucositis, Crohn's disease, Melkersson-Rosenthal syndrome.

INTRODUCTION

The connection between the oral cavity and systemic diseases has become increasingly emerging over the past decade. As underlined by oral mucositis in this chapter, therapies for systemic diseases can also cause specific clinical pictures. Similarly, oral pathology can significantly alter the general health of the organism; a classic example is chronic inflammatory periodontal disease in a diabetic patient. For this, a correct anamnestic collection of the patient by the dentist is decisive. However, the patient does not always come with a diagnosis of systemic pathology, so the dentist plays a key role in referring the patient for further evaluation in case a systemic pathology is suspected. In this chapter, based on our clinical experience, we have dealt with Crohn's disease, Melkersson-Rosenthal syndrome, and chemotherapy-induced mucositis in cancer patients.

Crohn's Disease

Crohn's disease (CD) is a chronic inflammatory bowel disease that affects the entire gastrointestinal tract, particularly the last part of the small intestine and the

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colon [1 - 3]. Estimates of incidence globally vary significantly. However, an increase in incidence can be seen in the United Kingdom, Italy, Iceland, Finland and the United States, which doubled between 1955 and 1995 [4]. Particularly, areas with low incidence and prevalence have observed a steady increase in rates of inflammatory bowel disease, almost paralleling their urbanization [5 - 7]. CD occurs more in women than in men [8]. A recent systematic review found that the percentage of women affected ranged from 48% to 66% [8]. CD has a multifactorial etiopathogenesis with genetic, environmental, infectious and immune implications [9 - 11]. Some studies suggest that Crohn's disease results from a genetic predisposition, regulatory defects in the immune system of the intestinal mucosa and environmental triggers [12]. The literature shows that CD affects Ashkenazi Jews three to four times more than non-Jewish populations [13 - 17]. In contrast, African American and Asian people have a lower risk of developing CD [18]. Protective factors for CD development include childhood contact with animals, breastfeeding and rural life [14]. Among environmental factors, cigarette smoking is associated with a two-fold increase in the risk of Crohn's disease (odds ratio 1·76; 95% CI 1·40–2·22) [19]. Regarding medications, oral contraceptives [20], nonsteroidal anti-inflammatory drugs, aspirin [21], and increased use of antibiotics [22] increases the risk of developing CD. In contrast, statins, especially in elderly patients, result in a reduction in the CD development [23]. A diet high in saturated fats and low fiber consumption also increases the risk of CD development [24]. Patients affected by CD show a notable dysbiosis, with an increase in Gammaproteobacteria and Actinobacteria and a decrease in Firmicutes and Bacteroides [25]. Clinical CD is extremely heterogeneous; usually chronic diarrhea, abdominal pain and cramps, malabsorption, weight loss, low-grade fever and anemia are commonly found [26, 27]. Extra-intestinal manifestations can affect up to half of affected patients and even precede the diagnosis [28, 29]. The most frequent are arthritis, skin lesions, conjunctivitis, anterior uveitis, and episcleritis [28, 29]. The diagnosis is based on clinical and laboratory criteria, as well as on the correlation of histopathological findings [30]. CD oral manifestations are common and typically manifest as a noncaseous granulomatous inflammation [31 - 33]. The mucous membrane of the oral cavity has a typical “pebbled” appearance, a sign of the nodular and granulomatous swelling of the oral mucosa (Fig. **1**) [34 - 37]. Often, as in our case, there are fringe-like polypoid exophytic neoformations of the inner lip and the retromolar region [35, 38, 39]. The lips often appear edematous; on palpation, they appear soft and painless [40 - 45]. Edematous lips often develop painful vertical fissures that can cause secondary bacterial and fungal infections [46]. In addition, the literature shows that non-specific oral signs such as irregular erythematous patches on the cheek mucosa, oral candidiasis, exfoliative, and angular cheilitis can raise the CD suspicion [47]. The diagnosis is histological.

Drug therapies for CD include antibiotics, topical or intralesional steroids, monoclonal antibodies, and cheiloplasty, with different outcomes depending on the follow-up period [41, 48, 49].

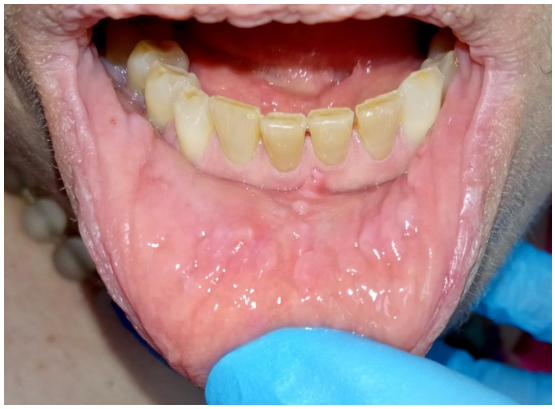

Fig. (1). Typical "pebbled" appearance with nodular and granulomatous swelling of the labial mucosa in a patient with Crohn's disease.

Melkersson-Rosenthal Syndrome

Melkersson-Rosenthal syndrome is a rare syndrome characterized by a triad consisting of orofacial swellings, recurrent facial nerve paralysis, and a fissured tongue [50 - 54]. This triad is not always complete, and the disease can present in an oligosymptomatic form with only lip swelling. In the case of labial localization, the disease has been called granulomatous cheilitis or Miescher's disease (Fig. **2**) [55 - 57]. Melkersson-Rosenthal syndrome affects young adults between the ages of 25 and 40, with a 2:1 predilection for women. This syndrome is rare in children [58, 59]. The etiology of this syndrome remains unknown. A possible relationship with hereditary granulomatous diseases, diabetes mellitus, chronic and/or mycobacterial infections, HSV-1, thyroiditis, keratitis, psoriasis, sarcoidosis and Wegener's granulomatosis has been reported in the literature [58, 60, 61]. In some patients, the onset was related to allergic phenomena caused by certain foods (chocolate, glutamate monoxide). Clinical manifestations mainly affect the lip in 75% of cases. Labial swellings can affect only the upper lip, the lower lip, or both. When the swelling becomes extensive and persistent, a protrusion develops associated with fissuring of the midline or labial commissures [62, 63]. The labial mucosa can become erythematous and undergo a desquamation process [19]. Furthermore, Snoussi *et al*. reported the case of a young woman affected by CD with gingival hyperplasia, which can be identified as a rare clinical feature [64]. Diagnosis must always be based on the correlation of clinical and histopathological data. In the case of patients who show gastrointestinal involvement, it is always necessary to exclude Crohn's disease

CHAPTER 5

Labial Vascular Diseases

Abstract: Malformative lesions of vascular origin should be considered among the neoplasms of the facial soft tissues. These comprise a very heterogeneous group that can be classified into tumors and vascular malformations. Vascular malformations are characterized by a structural defect of blood vessels that have a physiological turnover of endothelial cells resulting from a malformation during development. They can, in turn, be sporadic or associated with genetic mutations. They are classically divided into low or high-flow vascular malformations. The former have no arterial component and are classified according to their predominant endothelial cell type as capillary, venous, lymphatic or combined. The latter has an arterial component and includes arterial malformations, arteriovenous malformations, arteriovenous capillary malformations and arteriovenous fistulas. Vascular tumors include benign and malignant neoplasms of endothelial cellular origin. Among the most common vascular tumors, hemangioma stands out. Pyogenic granuloma (lobular capillary hemangioma) is the most commonly diagnosed subtype of benign endothelial neoplasia in the oral cavity. Furthermore, most oral pyogenic granulomas are considered reactive rather than neoplastic proliferations. Among the malignant ones, much rarer, Kaposi's sarcoma and angiosarcoma emerge.

Keywords: Malformative lesions, Pyogenic granuloma, Vascular malformations, Vascular tumors, Venous lake.

INTRODUCTION

In this chapter, we have discussed the benign vascular malformations of the most frequent clinical finding. The nosological classification of vascular anomalies is still a source of considerable difficulties and controversies due to the heterogeneity of clinical-pathological entities and the confusion generated by the medical terminology of the past. The classification that we have decided to opt for is the one dating back to 1996 by the International Society for the Study of Vascular Anomalies (ISSVA). This classification has the advantage of being very simple and schematic. It distinguishes vascular anomalies into two main groups that radically differ on the anatomical-pathological level: vascular tumors, which are neoplastic pathologies, and vascular malformations proper, which consist of disembryogenetic alterations of various districts of the circulatory system. Furthermore, the vascular malformations are divided, in relation to the hemodynamic characteristics, into two main subtypes (high flow and low flow) to

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which complex or combined forms are added. Clinically, most vascular lesions of the oral mucosa are small and superficial, but sometimes, they can involve deep submucosal structures and be of considerable size. Deep-lying lesions may appear normal in color, while superficial presentations are dark, usually blue-purplish in color. A decisive aspect is the positivity to the diascopy; when a slight pressure is exerted, there is a whitening of the mucosa.

Labial Vascular Diseases

Venous Lake

A venous lake, also known as senile hemangioma or phlebectasia, is a frequent benign vascular disease due to the dilation of pre-existing vessels [1 - 3]. The prevalence of this condition rises with increasing age and sun exposure [4]. Clinically, they appear as small papules 2 to 10 mm in diameter, usually solitary, soft and compressible, with a dark-blue to violaceous color (Figs. **1** and **2**) [4]. The lower lip is more involved than the upper one. Some venous varices can mimic pigmented lesions (especially labial melanotic macule and oral malignant melanoma), but the decrease in color intensity on diascopy allows for differential diagnosis [4]. Furthermore, no pulsation should be felt on palpation, which signifies that it is an arterial vessel coming from the labial artery [5]. In most cases, they are asymptomatic, but occasionally, they can be painful or bleed following even minor trauma. In the latter cases, especially if they worsen the patient's quality of life, they can be removed. Traditional treatments include surgical excision [6], sclerotherapy [7], cryosurgery [8 - 10], and infrared coagulation [11]. Laser therapy has recently proved effective in the treatment of lingual venous lakes [12 - 16]. The literature reports that long-pulse 1064 nm neodymium-doped yttrium aluminum garnet (Nd: YAG) appears to be effective in the treatment [16 - 20].

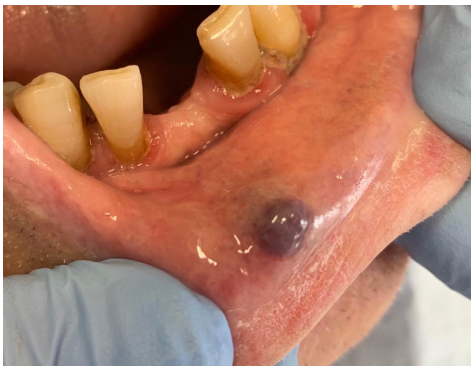

Fig. (1). Labial venous lake in an elderly male patient.

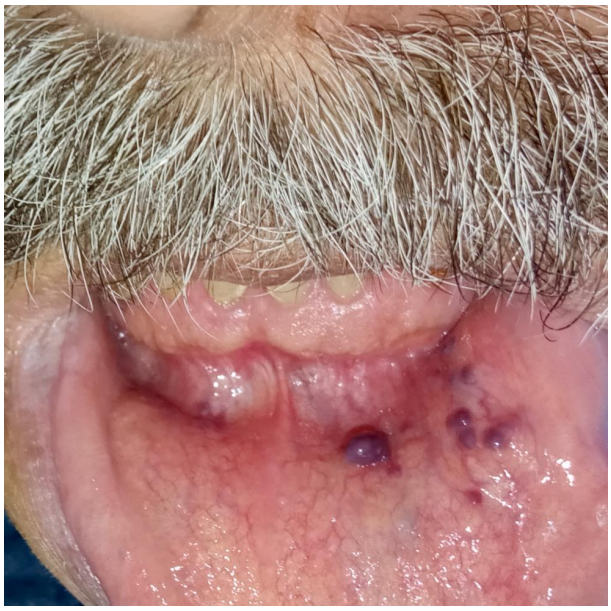

Fig. (2). Multiple labial venous lakes in a male patient on anticoagulation therapy.

Vascular Hemangioma

Vascular malformations are benign lesions characterized by a proliferation of blood vessels, relatively common in the head and neck region [21]. According to the classification of the International Society for the Study of Vascular Anomalies, hemangiomas can be either congenital or infantile [22]. Infantile hemangiomas are common in childhood [23]. They are characterized by a period of growth (usually during the first months of life) followed by a phase of spontaneous involution. Precisely for this reason, they do not require treatment in most cases unless they are symptomatic during the growth phase (for example, in case of ulceration or cosmetic impairment) [21]. Infantile hemangiomas have a prevalence of about 4.5%, with a preference for the female gender [23]. Risk factors include low birth weight, intrauterine complications (eclampsia, placental abnormalities), and advanced maternal age [24]. The most common complication is ulceration, especially in the perioral area, which can appear even before a clinically evident development [25]. Some forms of infantile hemangiomas may be associated with syndromes, especially when they have a segmental distribution [25]. The clinical signs are papular, nodular lesions, or raised plaques (Fig. **3**) [23]. Conversely, congenital hemangiomas are present and fully developed at birth; in fact, they can be diagnosed or suspected during the last trimester of intrauterine life [21, 25]. They are rarer than childhood ones [25]. The classic division is into two major subtypes: rapidly involution congenital hemangiomas and non-involutive congenital hemangiomas [21]. Most of the former evolve

CHAPTER 6

Labial Potentially Malignant Disorders and Cancer

Abstract: Labial potentially malignant disorders of the oral cavity are one of the main risk factors for the onset of oral cancer. Oral cancer now accounts for 3-5% of malignant tumors in Western world statistics. For this reason, the treatment of precancerous diseases of the oral cavity assumes an undeniable importance in preventing the onset of this pathology. Pre-cancers of the oral cavity include the forms with the highest risk of malignant transformation (erythroplasia, homogeneous and non-homogeneous leukoplakia) and the other forms with a low index of malignant transformation (lichen planus, oral submucosal fibrosis, leucoplakia, and chronic hyperplastic candidiasis). The cause of the onset of the precancerous oral cavity is unknown, but there are usually some risk factors that, alone or in combination, play an action favoring the appearance of the mucosal lesion. The main risk factors for precancerous lesions in the oral cavity are tobacco, alcohol, chronic local trauma, poor oral hygiene, chronic dietary and vitamin deficiencies, exposure to diagnostic and therapeutic ionizing radiation, viral and fungal infections and immunological factors. In this chapter, we will focus on actinic cheilitis, an extremely common precancerous condition of the lips, and oral cancer.

Keywords: Actinic cheilitis, Labial potentially malignant disorders, Oral submucous fibrosis, Squamous cell carcinoma, Verrucous carcinoma.

INTRODUCTION

Labial potentially malignant disorders of the oral cavity are one of the major risk factors for the onset of oral cancer. Carcinoma of the oral cavity nowadays represents 3-5% of malignant tumors in the Western world. For this reason, the diagnosis and treatment of precancerous lesions in the oral cavity assume undoubted importance in preventing the onset of oral cancer.

Precancerous diseases are defined as “tissue alterations that, although not presenting the biological and histological alterations typical of neoplasms, can develop malignancy”.

Particularly, the WHO defined precancerous labial potentially malignant disorders of the oral cavity as “morphological alterations of the mucosa referable to local expressions of generalized diseases (precancerous conditions), or to localized reactions from chronic irritative factors, which have a probability of degenerate

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greater than that of the surrounding normal mucosa ". The precancerous transformation usually occurs in the epithelial component of the mucous membrane of the oral cavity. Pre-cancers of the oral cavity are a heterogeneous group of pathologies, presenting different characteristics both in appearance and clinical presentation and in the potential for evolution in a malignant sense. Pre-cancers include previously treated lichen planus, oral submucosal fibrosis, leucoplakia and chronic hyperplastic candidiasis. The main risk factors for oral precancerous diseases are tobacco, alcohol, chronic local trauma, poor oral hygiene, dietary and chronic vitamin deficiencies (vitamins A, B and C, sideropenic anemia, trace elements), exposure to diagnostic and therapeutic ionizing radiation, work environment, viral and fungal infections (*Candida albicans*) and immunological factors (lichen, autoimmune bullous diseases). In general, the risk factors can lead to changes in the cellular genome as the initiation of oncogenesis (precancerous condition), while otherwise, they can cause irreversible changes in cellular reproductive activity and any atypia (precancerous lesion). The incidence of oral precancerous diseases shows variations in different countries based on the numerous risk factors, often linked to the voluptuous habits of the local population, which intervene in their onset.

Epidemiological studies indicate that the precancerous oral cavity affects 5-15% of the adult population in the western white race. From an epidemiological point of view, the geographical distribution comparable to that of carcinoma of the oral cavity is significant. The increase in incidence is parallel to the progressive increase in the age of patients (precancerous diseases are a typical pathology of decades beyond the fourth) and the absence of a clear sex predilection to the exclusion of those populations with voluptuous habits such as, the chewing of tobacco by men in India. In this text dedicated to the pathologies of the oral cavity, we could not treat actinic cheilitis, an extremely common precancerous condition of the lips. It follows a brief discussion on oral cavity carcinoma, the most frequent malignant neoplasm in this anatomy area, which represents about 90% of all malignant neoplasms.

Actinic Cheilitis

Actinic cheilitis (AC) is a chronic lip pathology that most often involves the lower lip, resulting from excessive exposure to solar UV radiation [1 - 3]. Additional risk factors are a clear phenotype, recreational and work activities involving high sun exposure, male gender, advanced age, genetic factors and immunosuppression [4]. AC is considered a potentially malignant lesion. A systematic review of observational studies on malignant transformation of actinic cheilitis is given [2]. In fact, a recent study of the literature found that out of 124 cases, 60.5% had dysplasia, and 25% had carcinoma [5]. The reported overall prevalence is

variable, ranging from 2.5% to 4.5% [6, 7]. As regards clinical features, AC may appear as a white lesion, ulcer or scab accompanied by erythema, peeling and dryness (Figs. **1**-**3**) [8, 9]. In addition, men over the age of 50 are more frequently affected than women, mainly due to higher occupational exposure (Fig. **4**) [7, 9 - 11]. For this reason, it is always useful to obtain a careful medical history for the evaluation of associated risk factors in a patient with a long-standing lip lesion. The diagnosis of AC is simple, as it is based on the assessment of risk factors, an ab accurate clinical history, and physical examination. Poitevin *et al*. [12] proposed an AC clinical score divided into four grades:

- Grade I: Dryness and flaking of the labial vermilion.
- Grade II: Atrophy (pale areas, rashes and soft surfaces) of the vermilion border, with the border between vermilion and skin blurred.
- Grade III: Rough and scaly areas on the driest parts of the vermilion and hyperkeratotic areas that extend to the internal labial mucosal surface.
- Grade IV: Single or multiple ulcerations of the vermilion, especially in areas subjected to trauma (for example, from the use of a pipe or cigarette).

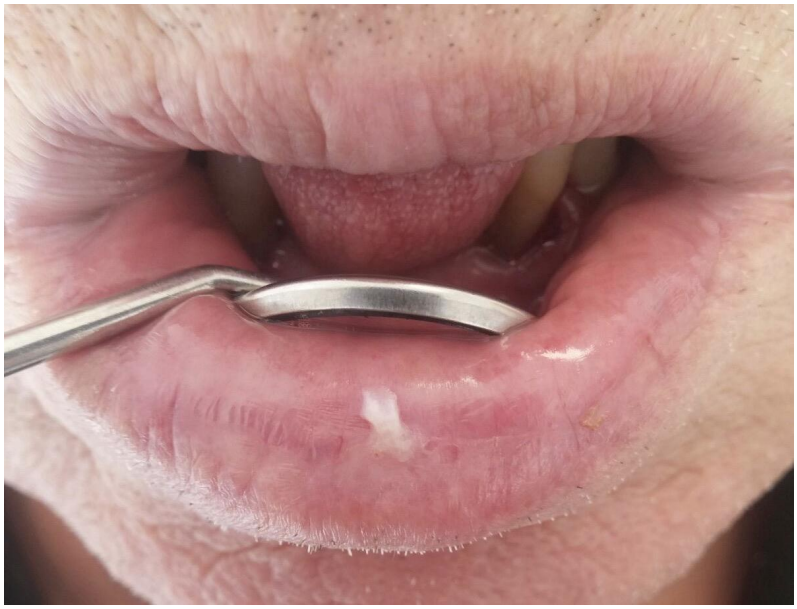

Fig. (1). Actinic cheilitis clinically characterized by inferior labial leukoplakia in an adult smoker and drinker.

CHAPTER 7

Labial Pigmented Lesions

Abstract: The diagnosis of oral mucosal pigmentations is complex, and histopathological evaluation may be necessary to clarify the nature of the lesion. Although most oral pigmented lesions are benign, it must be emphasized that melanoma of the oral cavity, probably the most aggressive epithelial tumor, is often underestimated and diagnosed late. The dentist, therefore, should have basic knowledge of the main epidemiological and clinical characteristics of this large group of lesions. Pigmented lesions associated with melanin include racial pigmentations, melanotic macules, smoking-associated melanosis, melanocytic nevi, melanoacanthoma, and melanoma. Some systemic diseases (for example, Peutz-Jeghers syndrome and Laugier-Hunziker syndrome) are also characterized by the presence of melanin lesions in the oral mucosa. In the literature, there are also some cases of pigmentation caused by melanin in association with the intake of drugs and as a consequence of some post-inflammatory mechanisms. Pigmented lesions not associated with melanin are subdivided according to the nature of the pigment responsible for the discoloration. The pigmentations caused by the deposition of exogenous pigments are represented by some metals (for example, amalgam, tattoo), drugs, or their metabolites.

Keywords: Melanotic macules, Nevus, Pigmented lesions, Racial pigmentations, Smoker's melanosis.

INTRODUCTION

Pigmented lesions can be expressions of both physiological and pathological conditions [1 - 9]. These lesions can be physiological but can also have a neoplastic [10 - 13], iatrogenic [14], reactive etiology [15, 16], or be a clinical manifestation of systemic pathologies [17 - 23]. For this, pigmented lesions can be classified into two large groups: one group containing melanin and the other group due to pigmentations from exogenous substances. Melanocytes, which arise from the neural crest, are dendritic cells located between the basal cells and the cytoplasmic extensions that insinuate themselves between the suprabasal cells.

Typically, one melanocyte is observed for every 20-30 basal cells. The melanocytes produce melatonin granules, which migrate along the extensions and are picked up by the adjacent keratinocytes. A wide variety of pigmented lesions are observed in the oral cavity, which can be caused either by an increase in melatonin production or by an increase in the number of melanocytes. The locali-

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zed deposit of melanin gives rise to the macula, while the benign and malignant proliferation of melanocytes gives rise to nevi and melanoma, respectively. Pigmented lesions can also derive from the deposit of exogenous substances introduced accidentally, as happens, for example, in the case of amalgam or tattoos. Certain physiological conditions, such as pregnancy (melasma gravidarum), can cause hyperpigmentation of both the skin and the oral mucosa. Melanin hyperpigmentation can be observed under physiological conditions in dark-skinned individuals. The various localizations and manifestations of the pigmentations of the oral mucosa, and in particular, of the labial mucosa, make it difficult to distinguish those attributable to systemic diseases, inflammatory diseases, neoplasms, drugs or heavy metal poisoning, or tattoos due to dental materials. The purpose of this chapter is the clinical, histological and immunophenotypic identification of the various hyper and hypopigmentations.

PHYSIOLOGICAL CONDITIONS

Melanotic Macules

Melanotic macules are benign pigmented lesions that most frequently involve the gingival mucosa and lips [24], especially the lower ones [2, 25, 26]. Melanotic macules result from increased production of melanin and, occasionally, also melanocytes [27 - 31]. These lesions usually develop in adulthood, on average during the fourth and fifth decade of life [2, 24, 26, 29, 32, 33], although they are more rarely seen in pediatric patients [34 - 38]. In addition, the female:male ratio is 2:1 [2, 26], although Gupta *et al*. reported a female:male ratio of 5:1 in a review of 79 cases [39]. The site most involved is the lower lip, as reported by numerous studies in the literature [32, 39]. It is particularly important to highlight that patients with a light phenotype are more likely to develop melanotic macules in the lower lip than dark patients in the oral cavity [32]. The clinical manifestations are focal lesions of well-circumscribed shape, usually oval or rounded (Figs. **1** and **2**) [2, 40]. Melanotic macules can be single or multiple [39, 41, 42]. The color is usually homogeneous, blue or brown-black, with a diameter of less than one centimeter [40]. Dimensions vary but are generally less than 1 cm [29, 33, 43]. It is important to underline that melanotic macules larger than one centimeter in diameter, asymmetrical, and with an uneven color should be considered suspicious for melanoma in the context of a labial macula [40, 44]. Furthermore, a curious aspect is that melanotic macules, unlike ephelides, do not become darker following sun exposure [2]. Diagnosis is usually clinical, and no treatment is needed. However, in doubtful cases, biopsy and histopathological examination are essential for a correct diagnosis [45 - 49]. The literature, however, reports the use of laser therapy for the treatment of melanotic macules, especially for aesthetic reasons [50 - 53].

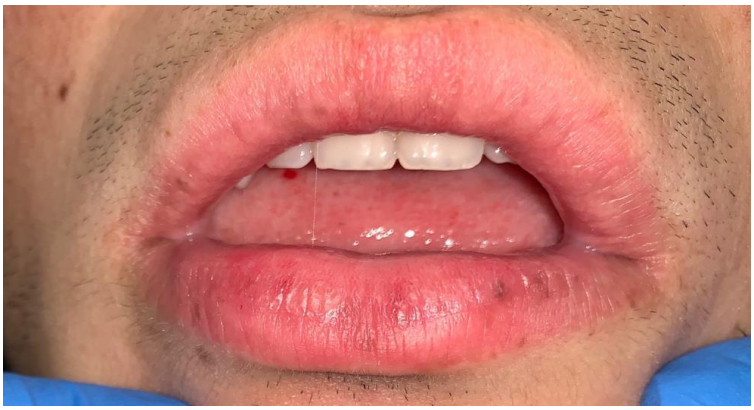

Fig. (1). Multiple melanotic macules in a young boy.

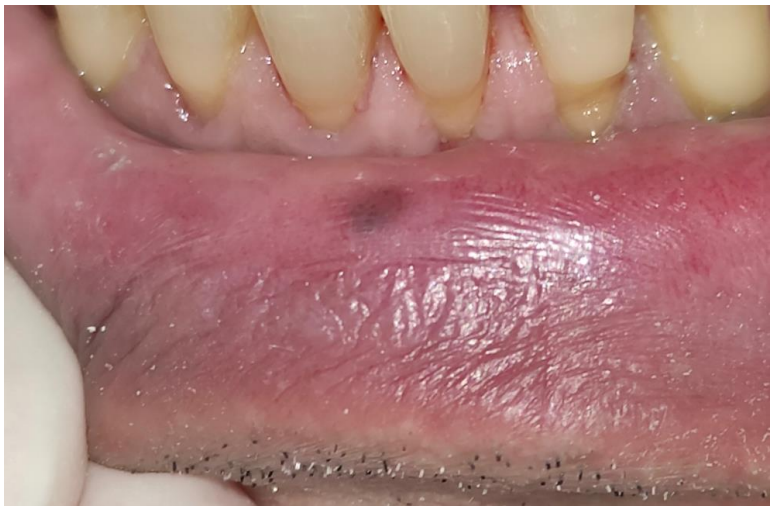

Fig. (2). Solitary melanotic macula in an adult male.

Racial Pigmentation

Racial pigmentations are benign pigmented lesions that occur more frequently in dark-skinned populations [2, 54 - 56]. According to an epidemiological study, the gingiva was affected in most cases (72%), followed by the buccal mucosa (46%), lip mucosa (26%), tongue (13%) and palate (4%) [57]. Physiological pigmentation is not caused by melanocytic hyperplasia but by increased activity [58, 59]. Clinically, it presents with diffuse pigmentations, brown in color, and faded margins (Fig. **3**) [2, 55]. Furthermore, in most cases, they are symmetrical and persistent and do not alter the normal architecture of the tissues [2, 55]. The clinical differential diagnosis should include smoking melanosis, Peutz-Jeghers syndrome, Addison's disease, and melanoma [56, 60]. Since it is a physiological condition, it is asymptomatic and does not require any treatment, except for

CHAPTER 8

Alternative Therapeutic Protocols for Lip Diseases

Abstract: Photodynamic therapy (PDT) is one of the most innovative therapies currently available with no side effects. Initially introduced for the treatment of dermatological pathologies, it is now used in numerous medical fields, as well as in oral pathology. PDT has antimicrobial effects and can be used in several infections. The mechanism of action of PDT is based on the application of a dye called photosensitizer, which is activated by a precise wavelength. The photosensitizer is activated by specific wavelengths based on the chemical characteristics. Its activation involves the formation of reactive oxygen species that determine the death of the altered cells. Phototherapy is a therapeutic medical treatment based on the use of a special optical unit capable of emitting light, which can be used with or without UV radiation. Phototherapy acts as a natural and non-invasive therapy, capable of transferring energy to the cells of the organism, promoting regenerative capabilities. The aim of our work is to report our clinical experience in the treatment of some lip pathological conditions with phototherapy and PDT.

Keywords: Herpes simplex 1, Lichen planus, Photodynamic therapy, Photosensitizers.

INTRODUCTION

Photodynamic therapy (PDT) is an alternative therapy based on the activation of a photosensitizer by a specific light, which determines the death of selectively altered cells [1, 2]. Photodynamic therapy needs three components: light of a specific wavelength, the presence of oxygen, and the photosensitizer [1, 2]. PDT is based on the formation of reactive oxygen species (ROS), which induce the death of microbial cells or damaged cells [3]. In fact, the activation of the photosensitizer can induce two processes: the formation of an oxygen triplet or the loss of energy, the latter in anaerobic conditions [4]. From the interaction between oxygen and photosensitizer, the following can be formed: hydroxyl radicals (-OH), hydrogen peroxide (H2O2) and singlet oxygen (-O) [4]. These metabolites induce cell death [4]. The maximum light absorption value of the photosensitizer occurs with light that has a wavelength between 600 and 800 nm

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and produces enough energy to stimulate oxygen to produce ROS [4]. The wavelength penetration rangesfrom 700-1100 nm and is wider than 400- 700 nm [5].

Photosensitizers

A photosensitizer (PS) or chromophore is defined as a single ground-state compound with a photoactivating electron. In fact, it has conjugated unsaturated bonds that require specific wavelengths to activate [6]. The requirements of a good PS are chemical stability, production and quality-price ratio, stability in warehouse and transport processes, and absence of toxicity [6]. There are numerous types of PSs, both of synthetic and natural origin [4].

In the literature, curcumin, extracted from the roots of Curcuma Longa, appears to be the best-known PS. In fact, it has numerous applications, both in the food and cosmetic sectors. The chemotherapeutic, anti-inflammatory, antioxidant and antimicrobial capabilities are widely described in the literature [4]. In PDT, curcumin is activated by blue light with a wavelength between 405 and 460 nm [6]. Flavonoids are polyphenolic compounds that are secondary metabolites of plants containing a benzopyronic structure. In nature, these compounds are found in fruits, vegetables and some of their derivatives. Flavonoids have antioxidant, anti-inflammatory, anti-carcinogenic and anti-mutagenic properties [6]. The best-known flavonoid is quercetin, activated by light with a wavelength of 557 nm. Another well-known photosensitizer is riboflavin, which is present naturally in vegetables, milk, and egg whites. Riboflavin is activated at 360-440 nm wavelength. Among synthetic photosensitizers, phenothiazine, methylene blue and toluidine blue are the most widely used [6]. Methylene blue is an organic compound of the aromatic heterocyclic class. Methylene blue was used in the 1980s as a treatment for malaria, methemoglobinemia, and hepatopulmonary syndrome. This compound is activated at a wavelength between 63 and 680 nm [7].

Methylene blue has antimicrobial properties, especially against P. *aeruginosa, P. gingivalis, S. aureus, S. mutans and Aggregatibacter spp*., proving useful in the treatment and prevention of carious and peri-implant oral pathologies [7, 8]. The affinity of this dye with melanin was proposed for the treatment of melanoma with PDT protocol, and it is also recommended for the treatment of osteosarcoma with PDT [7]. Methylene blue has proven to be very useful in the treatment of herpetic oral infection. It has been documented that in patients with monthly herpetic recurrence rates, a single PDT session performed with methylene blue activated with a 660 nm diode laser is sufficient to reduce relapse drastically [9 - 13]. In the clinical field, toluidine blue can be used for diagnostic purposes for the

early evaluation of neoplasms, thanks to its high ease of use and good selectivity in the identification of tumor and pre-cancerous cells. It also generates false positives due to its affinity to bacteria; therefore, since about 15-20 years, it is not being used to evaluate the presence of oral cancer lesions. It has demonstrated a certain antimicrobial activity (documented overall with in vitro studies) against various microorganisms, especially against *Candida albicans*. Six hundred and thirty nm is the best-performing wavelength for the activation of toluidine blue. Different concentrations are proposed in the literature, but the most used is 1% [14]. Rose bengal and erythrosine are other widely used synthetic photosensitizers. They are halogenated derivatives of fluorescein. These photosensitizers are activated by light with a green wavelength between 480 and 550 nm [15].

Tetrapyrroles are a class of active chemical compounds that includes four smaller compounds with a ring structure, known as pyrroles, contained in the chlorophyll and the hemoglobin. The most frequently used of this group are porphyrins and phthalocyanines. Phthalocyanine is activated around 670 nm wavelength, while porphyrins between 405 and 550 nm [15]. *Porphyromonas gingivalis*, *Propionibacterium acnes spp*., *Aggregatibacter actinomycetemcomitans* and *Prevotella spp.* accumulate a high concentration of porphyrins. Therefore, if irradiated with UV or blue light, they undergo cell necrosis [15].

New Photosensitizers

Indocyanine green (ICG) is a tricarbocyanine used in diagnostic investigations of cardiac output, liver function, and hepatic blood supply for about 60 years [16 - 20]. If sodium iodide is added to ICG, it has a brown color; if diluted with water, it becomes green [17]. The peak of absorption is around λ = 875 nm. This photosensitizer is used in antimicrobial PDT of oral periodontal and S. mutans infections [21 - 24].

In recent times, the need to improve the effectiveness of all photosensitizers has led some researchers to amplify their activity by adding nanoparticles. Among these, the most added are gold, silver, silica derivatives, and metal oxides. Curcuma, methylene blue, toluidine blue and rose bengal are the photosensitizers most enriched in nanoparticles [25, 26].

Type of Lights

In PDT, 3 types of lights can be used to illuminate photosensitizers: laser, LED light, and lamps. The first consists of a light source characterized by a monochromatic and coherent light beam with a very precise and narrow bandwidth. A laser is composed of an active medium, *i.e*., a material that emits

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