Clinics in Dermatology Editors: Nasim and Rogers

Diseases of the Lips

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Abstract

Heath care providers should be comfortable with normal as well as pathologic findings in the lips as the lips are highly visible and may display symptoms of local as well as systemic inflammatory, allergic, irritant and neoplastic alterations. Fortunately, the lips are easily accessible. The evaluation should include a careful history and physical examination including visual inspection as well as palpation of the lips and an examination of associated cervical, submandibular and submental nodes. Pathologic and microscopic studies, as well as a review of medications, allergies and habits may further highlight possible etiologies. Many lip conditions, including premalignant changes are

relatively easy to treat when the abnormalities are detected early; however, advanced disease and malignancies are challenging for both the patient and clinician. Treatment should be focused on eliminating potential irritant or allergens and treatment of the primary dermatosis. In this article, we review physiologic variants as well as pathologic conditions of the lips.

INTRODUCTION.

Cheilitis refers to inflammatory, allergic, irritant, or neoplastic alterations of the lips occurs (Table 1). With inflammatory, allergic or irritant processes, patients complain of eroded or dry, cracked lips, that may or may not be swollen, but possibly painful or itchy. On physical examination, there may be slight edema to complete loss of the normal lip markings. With advanced inflammation, exfoliation, dry scale, and fissuring may occur. In contrast, neoplastic processes of the lips may be asymptomatic and present with mild color alteration, infiltration, nodularity, or ulceration (Table 2). Finally, it is not unusual for benign developmental variants of the lips to present with hypertrophy or swelling that raise concerns.

Most lip conditions, including premalignant changes, are relatively easy to treat, if abnormalities are detected early; however, advanced disease and malignancies are challenging for both the patient and clinician.

CLINICAL EVALUATION OF THE LIPS

The lips are innervated by motor divisions of cranial nerve VII. Lymphatic drainage is predominately to the submental and submandibular lymph nodes.

The lips, as are other surfaces of the mouth, are subject to trauma from food, chewing, and various habits. These changes may be difficult to differentiate from inflammatory and premalignant or malignant changes including leukoplakia, erythroplakia, erythroleukoplakia, and non-healing erosions. Fortunately, lip conditions are amenable to various diagnostic procedures such as visualization, palpation, microbiologic evaluation and biopsy. Because systemic and dermatologic diseases occur on the lips with considerable frequency, biopsy specimens can frequently be taken from the vermilion as well as the labial oral mucosa more easily and with less visible scarring than skin biopsies.[1, 2]

Evaluation should begin with a complete history and evaluation of the lips as well as the head and neck. Specific findings should focus on the history of onset and clinical course, followed by a thorough review of systems and complete mucocutaneous examination including the scalp/hair, palms, soles, nails and genitalia. A comprehensive review of topical and systemic medications, allergies and oral habits can be critical to targeting the

etiology of conditions of the lips. The history and examination findings should dictate further laboratory and/or histologic assessment.[1]

EXAMINATION OF THE LIPS

The lips should be evaluated both visually and digitally. The upper cutaneous lip extends from the base of the nasal columella to the vermilion border; the lower cutaneous lip extends from the vermilion border to the mental crease. The vermilion border is the slightly raised, linear, palpable junction between the skin and the vermilion. The vermilion of the lips is a hairless modified mucous membrane, pink to brown in color depending on the ethnicity, and covered by a thin dry stratified squamous epithelium. The lateral junction of the upper and lower vermilion lips defines the oral commissure (angle of the mouth). The labial mucosa begins at the wet-dry line where the vermilion and the mucosal junction meet. The labial mucosa is covered by nonkeratinized stratified squamous epithelium and extends to the sulcus of the dental arches.

Bi-digital palpation of the lips permits appreciation of multiple, freely movable 2 - 4 mm papules within the substance of the upper and lower lips. These papules represent normal accessory (minor salivary glands) which secrete myxoid saliva directly onto the labial mucosa.[1] To visualize the myxoid saliva, the clinician should gently dry off the mucosa using a piece of gauze as the lip is everted. Within 2-3 minutes, clear myxoid saliva pools on the surface of the lips. In contrast to the minor salivary glands, the paired major salivary glands express copious serous saliva from the parotid glands or mixed serous and myxoid saliva from the submandibular and sublingual glands.

The presence and quality of saliva can be further assessed by drying off the buccal mucosa gently milking the parotid gland by pressing on the outside of the cheek from the angle of the mandible in an anterior fashion, all the while looking for extrusion of saliva at Stensen's duct located across from the maxillary second molar. In contrast, saliva production by the submandibular and sublingual glands may be assessed by drying the floor of the mouth, pressing upwards at the submental/submandibular triangle, and inspecting for expression of saliva from Wharton's duct.[1] In patients with xerostomia, lack of myxoid or serous saliva pooling or cloudy saliva may be found.

DEVELOPMENTAL CONDITIONS OF THE LIPS

Lip prints, lip clefts, lip pits, and Fordyce granules

Lip prints are normal patterns seen on the vermilion of the lips that appear as folds, wrinkles, and grooves. The vermilion overlies minor salivary glands, while sebaceous glands line the distal border adjacent to the skin. Oil and moisture from these glands maintain the health of the vermilion. Because lip prints, much like fingerprints, are unique to each individual, they are often used in investigations at crime scenes.[3] Lip patterns do not alter with advancing age, inflammation, trauma, or environmental factors.[4] Multiple classification schemas have been identified in lip prints determined by the linear patterns.[5, 6] Lip prints even appear to be effective in gender differentiation.[6]

A number of developmental findings may be noted that help to understand the embryogenesis of lips. As the midface develops, the mandibular arch and the sulcus lateralis of the lower lip fuse. This is followed by fusion of the maxillary and nasofrontal processes. The most dramatic findings that are noted, when this normal process is interrupted are the development of clefts (1/700 births).[7] Cleft lip(s) result when there is an interruption in the normal fusion of the embryologic plates that form the lips and the palate early during embryogenesis.

Clefts may be limited to the lips or extend into the anterior hard palate. Palatal clefts may involve the hard and/or soft palate. In embryogenesis, the palate and the lips develop independently, thus clefts of the lips can occur with or without involvement of the palate and vice versa, or they may occur together. Cleft lips are most often unilateral, however, in rare instances they may be bilateral. The etiology of clefts is multifactorial and includes genetic predisposition, exposure to medications such as anticonvulsants,[8] isotretinoin,[9] methotrexate,[10] as well as complications secondary to viral infection (rubella).[11]

Lip pits (Van der Woude Syndrome, VWS) are other congenital findings of the lips. Pits are most often inherited in an autosomal dominant fashion.[12] These may occur in the setting of cleft lip and/or cleft palate or they may be independent. Pits may affect either the upper or more commonly, the lower lip and are most often located adjacent to the oral commissure or angle of the mouth. Pits may range in length from 1-25 mm and may involve the orbicularis muscle. Minor salivary glands may drain into these tracts resulting in mucous secretion from the pits.[13] Surgical resection is curative.

Fordyce granules (Fox-Fordyce spots) appear as small 1-3 mm yellow to orange or white papules. These ectopic sebaceous glands can be present on the vermilion of the lips, adjacent to the vermilion border, and more commonly on the labial and anterior buccal mucosa. They are often also found in the genital region.

Pigmented macules of the lips

Labial melanotic macules (focal melanosis) are benign pigmented macules on the vermilion. These pigmented macules may represent ephelides, post-inflammatory pigmentation, or the stigmata of Peutz-Jeghers syndrome or Addison disease. Melanotic macules may appear on any mucosal surface, however, most commonly are seen on the vermilion, palate, buccal mucosa, and gingiva. Macules may be blue, black, or brown. Typically, labial melanotic macules are solitary lesions, but multiple macules can occur. The labial melanotic macules are usually well-circumscribed and have an average diameter of 4-6 mm. Labial melanotic macules occur more frequently in women, and based on the authors' clinical experience may be more common in patients of Asian descent.

In labial melanotic macules, melanin accumulates in the basal keratinocytes without an increase in the number of melanocytes. Melanin in the lamina propria and melanophagocytosis may also be present. In contrast to oral nevi and malignant melanoma, labial melanotic macules are HMB-45 negative. Labial melanotic macules are asymptomatic and have no malignant potential.

Various medications may also cause macular pigmentation [14] Any lesion in question or those that are ulcerated, exophytic or variably pigmented should be excised to exclude malignant melanoma.

Hyperpigmented lesions of the lips and other mucosal sites are frequently encountered on routine examination. The significance of these lesions spans a wide gamut from a variation of normal to being a sign of an underlying life-threatening anomaly. The history and physical examination will help focus on possible conditions.

Physiologic melanoplakia is common in dark skinned individuals.

- Peutz-Jeghers syndrome is an autosomal dominant condition characterized by macular hyperpigmentation in early childhood and by hamartomatous polyps of the gastrointestinal tract.[15]
- Addison disease, or primary adrenal insufficiency, is characterized by diffuse hyperpigmentation of the skin and oral hyperpigmentation with a predilection for traumatized areas and skin folds as well as systemic findings that include weight loss, fatigue, hypotension and electrolyte abnormalities.[16]
- Albright syndrome is characterized by a triad of polyostotic fibrous dysplasia, precocious puberty, and pigmentary abnormalities of the lips.
- Laugier-Hunziker syndrome, a benign acquired syndrome, is characterized by solitary or confluent pigmented macules whose color may vary from gray to brown to blue-black.[17-19] These macules are commonly seen on the lower lip, hard palate and the tips of the fingers. The labial commissures, the gingiva and the floor of the mouth are less frequently involved.[19] Involvement of the fingernails, toenails and genitalia or perineum have been reported.[20] The nail pigmentation may appear as a single longitudinal streak; a double longitudinal streak in the lateral parts of the nail plate; or as homogeneous pigmentation of the radial or ulnar half of the nail.

In contrast to Peutz-Jeghers syndrome, Albright syndrome and Addison disease, there are no associated internal manifestations with Laugier-Hunziker syndrome. Histologically, Laugier-Hunziker syndrome is characterized by increased melanization of the basal keratinocytes and by an increased number of melanophages in the upper dermis. The melanocytes demonstrate normal morphology and number.

Lentigines are common brown macules that may appear on the palate, gingiva, and lips. They may be related to age and ultraviolet light exposure or may be seen in the setting of multiple lentigines syndrome (formerly termed LEOPARD syndrome). Microscopically, benign melanocyte hyperplasia is seen in conjunction with elongation of the rete ridges. Oral lentigines are probably not related to melanomas; however, if a labial melanotic macule enlarges one must consider lentigo maligna in the differential. Lentigo maligna, a rare form of malignant melanoma is typically found in Caucasian women. Lentigo maligna melanoma presents on the head and neck on sun exposed skin. Rarely, this tumor may extend onto the lips.[21]

Vascular Findings

Venous Lakes

Venous lakes of the lips are common blanchable blue to purple macules or papules that range in size from 2-8 mm. The lower lip is more commonly affected than the upper lip. The prevalence of these asymptomatic findings increases with advancing age and with sun exposure. Histologically, a single layer of flattened endothelial cells surrounded by relatively thick fibrous tissue is noted. No treatment is indicated as these rarely bleed but may be cosmetically offensive. In such cases, PDL laser or surgical excisions are effective.[22]

Caliber Persistent Artery

When evaluating the mucosal surface of the lip, a superficial tortuous vessel may be visible and is termed caliber persistent artery.[23] This common vascular anomaly occurs on the lower lip 80% of the time, but the upper lip and palate may also be affected. This developmental anomaly occurs when the inferior alveolar artery fails to taper as it exits the mental foramen and progresses superficially. The size and superficial location make the caliber persistent artery palpable, usually a few millimeters inferior to the vermilion border. Occasionally, it may appear as a sessile elongated nodule of variable size, which may raise concern for a benign or malignant tumor. Noninvasive high-resolution Doppler ultrasound may confirm the presence of an artery eliminating the need for biopsy.[24]

When the area is excised, the pathology reveals only a large artery with a thick, smooth muscle wall that is surrounded by variable fibrovascular connective tissue and stratified squamous epithelium. Pathologists should be made aware of the clinical differential, as the *in vivo* dilatation collapses upon excision thus appearing as a normal artery or arteriole with no visible pathology. Surgical excision may be associated with considerable bleeding that requires ligation of both transected vessel ends. In general, no treatment is indicated; some authors suggest that the finding of a caliber persistent artery on the lip may herald similar dilated arteries in the gastrointestinal tract associated with potentially lethal hemorrhage.[25]

TRAUMA-ASSOCIATED FINDINGS OF THE LIPS

Morsicatio Labiorum

Morsicatio labiorum (chronic nibbling of lips) is a self-inflicted mechanical alteration or habit that results from biting or sucking the lip. Morsicatio labiorum is more frequently noted on the lower lip than on the upper lip and presents with shredded or verrucous white plaques, zones of erythema, and erosions. [26] The shredded epithelium may be peeled off by the patient resulting in further trauma and ulceration. Frequently, the

anterior 1/3 of the buccal mucosa (morsicatio buccarum et labiorum) and/or lateral border of the tongue (morsicatio linguarum et labiorum) are also affected.[27, 28]

The patient may or may not be aware of his/her habit, but often, a family member or partner may be able to provide insight. Further questioning may also reveal concurrent stress, anxiety or other compulsive tendencies. Bilateral and often symmetric involvement in areas that are reachable by the teeth is diagnostic. In the context of the characteristic clinical presentation and distribution, a biopsy is unnecessary. If the presentation is not classic, then a biopsy should be performed.

The histopathology of morsicatio is diagnostic and exhibits an acanthotic and hyperkeratotic epithelium.[29] Numerous keratin projections are lined by basophilic bacterial organisms. Clusters of vacuolated keratinocytes may be present in the spinous cell layer. Special staining for fungi is negative. Microbial culture provides no benefit. The differential diagnosis includes oral pseudomembranous candidiasis, oral hairy leukoplakia and white sponge nevus of Cannon. Treatment, if desired, involves behavioral modification only.

Mucoceles

A mucocele is a benign pathologic entity of the minor salivary glands that result in myxoid saliva accumulation below the mucosal surface.[30, 31] Clinically, most mucoceles appear as a single but often recurrent, translucent, fluctuant 0.5-1.5 cm cyst-like pink, papular swelling on the lower lip. Other locations include the floor of the mouth, buccal mucosa, ventral tongue or soft palate. Due to the Tyndall effect, some mucoceles may appear bluish in color. The patient may note a thick myxoid/sweet-tasting extravasation with rupture of the mucocele. With repeated episodes, fibrous scarring may spread to adjacent glands with potential increased nodularity.

Two distinct mechanisms come into play in the onset of mucoceles. More commonly, mucoceles may result from traumatic rupture of a minor salivary gland duct with spillage into the surrounding submucosa (extravasation type). Less often, the minor salivary duct may become obstructed due to a stone (sialolith) resulting in retrograde accumulation of saliva within an epithelial capsule just below the mucosal surface (retention type).

The differential diagnosis includes a benign or malignant salivary gland neoplasm, hemangioma, lymphangioma, soft tissue abscess, lipoma, pyogenic granuloma or fibroepithelial polyp. Rarely, a limited manifestation of pemphigoid, pemphigus vulgaris, or herpes simplex virus infection may be considered, but the history and histopathology are diagnostic. Treatment, if necessary, includes excision, cryotherapy, or local administration of corticosteroids, all of which have been reported with mixed results.

INFECTIOUS AND INFLAMATORY DISORDERS OF THE LIPS

Angular cheilitis

Angular cheilitis (angular cheilosis, angular stomatitis, perlèche, derived from the French lécher meaning to lick) is characterized by painful fissures of the oral commissure(s) that extend from the mucosal surface to the cutaneous skin; maceration, erythema, crust and scale are often present. The pathogenesis is often multifactorial. Unilateral involvement tends to be short-lived and has been attributed most often to local trauma. (Figure 1)

Bilateral disease is often chronic and suggests an anatomic abnormality with overclosure of the mouth, irritant reactions, infections, inflammatory dermatoses and/or nutritional deficiencies.[32] Anatomic abnormalities in patients with ill-fitting dentures, malocclusion of the natural teeth and/or overclosure of the teeth predisposes to pooling of saliva at the commissures. Inadequate support of the lips, reduced occlusal vertical dimension and formation of static marionette lines with aging are additional risk factors.

Habitual lip licking (Figure 2), thumb sucking, lip biting and improper flossing may also predispose to angular cheilitis.[33] Patients undergoing orthodontic treatment may be susceptible due to contact allergy;[34] however, good oral hygiene reduces the risk of angular cheilitis in this population.[35] Particularly, in patients younger than 35 years old, angular cheilitis may be a presentation of oral psoriasis.[36] Angular cheilitis may also result from deficiencies in riboflavin (B2), niacin (B3), pyridoxine (B6), biotin (B7), folic acid (B9), cyanocobalamin (B12), iron, and zinc.[32, 37]

Medications rarely directly cause angular cheilitis.[38] Medications are more likely, however, to cause xerostomia (eg. anti-cholinergics) or exfoliative cheilitis (eg. isotretinoin, indinavir) and thereby predispose to the development of angular cheilitis.[39, 40]

The clinical differential diagnosis of angular cheilitis includes herpes labialis, impetigo, irritant cheilitis (lip licker's dermatitis), actinic cheilitis, allergic contact cheilitis, perioral dermatitis, verruca vulgaris, split papules of secondary syphilis and squamous cell carcinoma.

Initial management is aimed at identifying and rectifying any precipitating factors. Treatment should be tailored to the specific cause(s) identified. Dentures and other dental prostheses (such as partials) should be evaluated by the dentist for appropriate fit, and the dentition should be examined for proper occlusion. Oral hygiene regimens should be reviewed and revised as needed. Local skin irritation may be minimized by the frequent use of barrier agents such as petrolatum.

Xerostomia should be addressed with lifestyle measures and/or pharmacologic therapy. Topical formulations of antifungal agents with or without antibiotics may be effective in immunocompetent hosts. In patients with evidence of intraoral candidiasis, who are immunosuppressed or who fail to respond to topical therapy, systemic antifungal treatment should be implemented.[41] Antibiotic therapy should be directed against specific cultured organisms. For cases involving *Staphylococcus* or *Streptococcus* species, mupirocin ointment 2% is the treatment of choice. In cases of refractory or chronic angular cheilitis, patients should be evaluated for underlying systemic disease, including

diabetes mellitus, anemia, Crohn disease, HIV infection, nutritional deficiency, and malignancy.[42]

Herpes Labialis

Herpes simplex virus (HSV), a double stranded DNA virus, is one of the most common infections worldwide. Two strains of HSV have been identified. HSV-1 accounts for nearly all cases of oral herpes while most genital infections are due to HSV-2. Each strain may cause infections at either site, though it is rare for HSV-2 to cause recurrent herpes labialis.[43] HSV-1 seropositivity rates range from 60%-90% worldwide.[43-45]

Primary infection may present with pain, cheilitis, perioral vesicles, gingivostomatitis, pharyngitis, fever, and coryza, especially in young children. Most cases of primary HSV infection are asymptomatic, subclinical, or misdiagnosed as a nonspecific viral illness. Following the initial infection, the virus lies dormant in the sensory trigeminal ganglia. Reactivation (secondary infection) presents with a prodrome of pain and or tingling associated with local edema and a headache. This is followed by the emergence, within a day or two, of grouped clear papulovesicles. Over the next 5-10 days, the vesicles erode, crust and then resolve. Recurrent herpes labialis most commonly occurs on the vermilion and vermilion border (keratinized surfaces).

Triggers for recurrent herpes labialis may include: ultraviolet light, wind, trauma (e.g. dental procedures), stress, severe drug eruptions, menstruation, and fever.[46] Immunocompetent hosts may have a primary infection without any clinically apparent recurrences. [47] Most patients with recurrent herpes labialis have two episodes per year; however, 5%–10% of patients may have six recurrences or more per year. Secondary impetiginization of herpes labialis is common.

Immunocompromised hosts tend to have more severe and more frequent recurrences.[48] Both the WHO and the CDC classify a chronic herpetic mucocutaneous ulceration lasting more than one month as an AIDS defining illness. Rarely, HSV can cause systemic complications including encephalitis, meningitis, and eczema herpeticum.[43] Other clinical manifestations of HSV infection include herpetic whitlow, herpes gladiatorum, ocular herpes virus infections with risk of secondary corneal blindness.[43]

The differential diagnosis for HSV infection is based on the location and clinical course. Aphthous ulcers generally occur on nonkeratinized mucosa, and therefore not on the vermilion but recurrent HSV lesions typically occur on the keratinized mucosa of the lips. When HSV-1 is secondarily infected, impetigo may also be considered in the differential diagnosis. In immunosuppressed individuals with extensive disease, vesiculobullous disorders should also be considered.

The diagnosis of HSV infections can be confirmed with viral culture, direct fluorescent antibody studies (DFA), or viral polymerase chain reaction techniques (PCR). A Tzanck

smear assesses the presence of multinucleated giant cells. It is performed by unroofing a vesicle, using a #15 blade to scrape the base of the lesion, and placing the scraping on a glass slide. The smear is then counterstained with Giemsa, Wright, or Papanicolaou stain. The presence of multinucleated giant cells with molded nuclei is suggestive but not specific of HSV infection, as these may also be present in varicella-zoster virus infections (VZV).[43] Other herpes viruses (such as the Epstein Barr virus, cytomegalovirus, exanthem subitum virus, or Kaposi sarcoma virus) that commonly affect the oral cavity are less likely to present with lip involvement .

Serologic testing for HSV demonstrates a high prevalence and is more sensitive than a patient's history due to asymptomatic or subclinical disease.[45] One study demonstrated that only 6%-8% of patients with a history of herpes labialis were seropositive for HSV-2 only.[49] Up to 40% of HSV-1 seropositive patients have a history of symptoms of orolabial infection.[43] Another study showed that in the US, 20%-25% of adults are seropositive for HSV-2, though many are subclinical/asymptomatic with 90% denying any prior history of a genital HSV infection.[43, 50]

Primary HSV infections may be treated with acyclovir 400 mg PO five times daily for 5 days (both for adults and older children) or valacyclovir 1g BID for 10 days to shorten the duration of oral lesions and reduce viral shedding.[43,51] There are no data to support using famciclovir for treatment of primary HSV infection.[52]

Recurrent herpes labialis may be treated with antiviral agents when patients have frequent or persistent outbreaks. Treatment during the prodromal phase has been shown to decrease the duration of outbreaks and even prevent lesion formation.[43] Appropriate regimens include: acyclovir 200 mg five times daily for 5 days (decreases symptom duration), famciclovir 125 mg BID for 5-7 days (decreases duration of lesions), or valacyclovir 2000 mg BID for 1 day.[52]

Chronic suppressive therapy has been shown to prevent outbreaks, decrease viral shedding, and possibly reduce transmission.[43] Appropriate chronic suppression regimens include: acyclovir 400 mg BID, famciclovir 250 mg BID or valacyclovir 1000 mg QD.[52] Thrombotic thrombocytopenic purpura is a serious potential side effect especially with long term use of valacyclovir in patients with advanced HIV disease.[43]

Is this a problem for other patients? Not typically (gmw)

Topical antivirals have not been shown to provide more benefit than placebo in treating recurrent infections or preventing attacks;[46] however, a novel agent, Acyclovir Lauriad, a muco-adhesive tablet applied to the gingiva at the onset of prodromal symptoms, has been shown to be effective. It reduces duration (by an average of one day) and incidence of episodes, aborts episodes, and increases time to next recurrence.[53]

Laser phototherapy has been shown to decrease pain, increase disease free intervals, viral titer, and drainage from the vesicles.[54] Lasers do not completely eliminate HSV and its recurrences, the process may be painful for patients, and it is unlikely to be covered by

insurance.[54] One major advantage of laser treatment is that there are no side effects and that drug-drug interactions may be avoided.[54]

Patients should avoid triggers, when possible, for example, by avoiding sun exposure, stress, wind, and trauma. Sunscreen use has been shown in several studies to reduce the frequency of recurrence of herpes labialis.[46] Patients may also take short-term prophylactic therapy prior to events known to initiate a recurrence, such as a dental procedure or skiing.[43] Secondary conditions, such as atopic dermatitis, should be treated early and aggressively.

Other viral infections of the lips

The human papilloma virus (HPV) is a naked double-stranded DNA virus that causes verrucous papules (squamous papillomas, verruca vulgaris, and focal epithelial hyperplasia or Heck disease). The association with labial SCC has not been confirmed, despite such an association with genital SCC.

Molluscum contagiosum is a viral disease due to the poxvirus, a DNA virus. Clinically, umbilicated papules with a central dell may affect the skin as well as the vermillion of the lip. Histologically, intracytoplasmic inclusion bodies (Henderson-Paterson bodies) are pathognomonic in cytological smears. Immunocompromised patients are particularly at risk for chronic labial involvement.

INFLAMMATORY DERMATOSES OF THE LIPS

Exfoliative Cheilitis

Exfoliative cheilitis is a nonspecific term that describes several chronic conditions. It is characterized by chronic scale and irritation of the vermilion with the lower lip often more severely affected than the upper lip (chronic chapped lips). Patients may complain of dryness, itching, or tingling. Numerous causes of exfoliative lip findings include inflammatory dermatoses, such as atopic dermatitis (AD), psoriasis, and chronic irritant or allergic reaction to cosmetics and or flavorings (Table 1). Exacerbating factors include stress, chronic mouth breathing, lip licking or sucking, and lip picking or biting. Treatment with topical corticosteroids and topical calcineurin inhibitors may be effective depending on the underlying etiology. Secondary impetiginization may complicate the clinical presentation and must be treated.

Atopic Cheilitis

AD is a common chronic pruritic condition that waxes and wanes. Patients with an atopic diathesis, which includes asthma, allergic rhinitis, and dermatitis, are commonly affected. Cutaneous clinical findings range from acute eczematous vesicular eruptions to subacute crusting and scaly rashes. AD is a very common associated diagnosis in children with

cheilitis. Cheilitis is one of the minor criteria in the Hanafin-Ruska criteria for diagnosing AD. [56] Chronic changes of the perioral skin and lichenification in the setting of an atopic history may be the only clues to the diagnosis. Suggestive serologic studies include eosinophilia and elevated serum IgE level; no diagnostic laboratory tests are available. Some authorities have suggested that a median fissure of the vermilion is highly suggestive.[55, 56] In patients with AD, the exposure to HSV may result in the generalized, life-threatening condition eczema herpeticum, (Kaposi's varicelliform eruption).

Allergic Contact Cheilitis

Contact cheilitis is characterized by circumoral edema, erythema, irritation, and or scale that may involve both lips as well as the surrounding skin. Contact cheilitis may be due to an immunologic allergic reaction or more commonly may be due to an irritant reaction (Table 3). Likely culprits include personal care products, balms, aerosol products, medicaments or foods.

The most common causes of contact cheilitis include the use of personal hygiene products such as toothpastes and mouthwashes, which contain numerous anti-bacterial agents, essential oils, and preservatives.[57,58] Mouthwashes also contain alcohols and propylene glycol.[59] It is hypothesized that saliva contributes to dilution or elimination of allergens resulting in lip involvement without intraoral findings. Personal care products often contain a long list of ingredients including menthol, clove oil, pimento oil, anise oil, camphor, phenol, lanolin, cocoa butter, salicylic acid, vitamin E, Shea butter, and sunscreens. Not all ingredients are present in all formulations. A subtle source of exposure to irritants and allergens are the personal care products of partners.[60]

Cosmetics, including lipstick, lip gloss, salves/balms and emollients, contain flavoring, dyes, preservatives/antioxidants, and sunscreens, as well as perfumes and pigments, which can cause contact cheilitis.[61] Hair sprays, facial creams and lotions, as well as nail polish, can also contribute to lip reactions. Foods, including carrots, orange peel, mango peels, coffee, and menthol, as well as cloves, curry, vanilla, nutmeg, paprika, mint, and others and, flavorings such as *Myroxylon pareira* (balsam of Peru), citral, cinnamaldehyde, peppermint oil, and geraniol, are well documented causes of cheilitis.[57, 62] Ricinoleic acid, a constituent of castor oil, has been identified as the commonest current cause of allergic contact cheilitis due to lip cosmetics.[63] Chewing gums and candies also contain many flavorings and thus are other common causes of contact cheilitis.

Personal habits, such as the use of nail polish and, cigarette holders, mouth guards, or chewing on pencil and pencil erasers, (rubber or nickel) and hairpins or metal tools, may result in cheilitis. Musicians who place their instruments in the mouth, such as wind and reed players, are particularly susceptible to the development of both irritant and allergic cheilitis.[64,65, 66] Topical medications including corticosteroids, benzocaine, and antibiotics have resulted in iatrogenic induction of cheilitis.[62] The use of dental materials, such as rubber dams and rubber accelerators in the fabrication of dentures as well as the presence

of eugenol in periodontal dressings and impression pastes, may contribute to acute cheilitis. Lastly, even if the patient is not using any suspicious agents, connubial exposure can result in cheilitis.

Treatment should focus on changing or discontinuing any suspicious products. Suspicious foods, candies and gums or cosmetics should be eliminated. All dental, orthodontic. or athletic appliances should be withheld and then reintroduced one at a time once the cheilitis has resolved. To help identify specific allergens, patch tests or use tests should be performed. Material data sheets may be obtained to further direct the clinician to likely allergens in braces or wires, which may contain nickel. Then, the dentist or orthodontist will need to identify non-nickel alternatives and remove offending appliances. The use of topical cortocosteroid ointment BID to QID and emollients should also be recommended. One caveat is that, allergic contact cheilitis can be caused by topical corticosteroids or emollients as well as preservatives and flavorings. When the lips get worse rather than better, consider an allergic contact reaction to the topical emollient or corticosteroid.

The histopathology of contact cheilitis reveals a nonspecific acute or chronic lichenoid dermatitis or mucositis with or without the presence of eosinophils and plasma cells.

Cutaneous patch testing is an essential part of diagnosing presumed allergic contact dermatitis. The North American Contact Dermatitis Group recommends a standard panel that is comprised of a series of allergens that includes common fragrances, metals, preservatives, and medications,[67]

Lupus erythematosus

Discoid lupus erythematosus (DLE) is the most common manifestation of lupus erythematosus. DLE typically present on the skin but may also present in the oral cavity and affect the lips.[68] (Figure 3) Most patients present in their early 50's with a female predilection of 8:1. Distinctive oral plaques of DLE appear as "sunburst" red and white plaques with characteristic peripheral radiating striations on the buccal and labial mucosal. Red and white oval plaques may also affect the vermilion.[69] Although both lips may be affected, the lower lip, possibly due to increased trauma or increased exposure to UV light, is affected in 71% of cases.[68, 70]

The clinical picture of DLE is nonspecific. Patients present with whitish lichenoid papules and plaques on the vermilion typically in the setting of either cutaneous and or intraoral involvement. This picture may be difficult to distinguish from lichen planus or even actinic cheilitis; however, despite this benign appearance, DLE of the lips can be associated with malignant transformation as documented in numerous studies.[71] In a literature review, almost half of SCC that arose in patients with DLE had lip SCC.[72] Associated risk factors such as smoking and alcohol, use were not found to be significant.[71]

Aggressive sun protection is needed in these patients. A biopsy is indicated due to the

aggressive nature if malignant transformation should occur.

Sjögren Disease and Xerostomia

Sjögren disease (SD) is an autoimmune systemic disease characterized by a dry mouth and dry eyes. Patients may have mild dryness of the lips. Multiorgan system disease can occur including the central nervous system, lungs, kidneys, GI tract, liver, pancreas, joints, and vasculature. SD is one of the most prevalent autoimmune disorders with 3.9 per 100,000 affected in the U.S.[73] Nine out of 10 patients are women.[74]
Sjögren disease may occur in isolation (50% of patients) or in conjunction with other autoimmune connective tissue disease, such as rheumatoid arthritis, lupus erythematosus, or scleroderma.

Decreased salivary flow may result in difficulties with speaking or eating and may be quite painful. Symptoms may remain steady, worsen, or remit over time. Symptoms and signs of SD may be nonspecific and subtle resulting in a delay of diagnosis or misdiagnosis with an average delay of 4.7 years.[75,76] SD patients are at risk for a variety of complications including weight loss, nutritional deficiencies, dental caries, and oral candidiasis. Early diagnosis and proper treatment may reduce serious complications and often improve patients' quality of life.

Diagnosis of Sjögren disease is made by performing a minor salivary gland biopsy [2,77]
For optimal diagnosis and care, multispecialty collaboration and communication including dermatology, ophthalmology, dentistry, gynecology, and others based on the clinical situation is essential.

Symptomatic care should include applying emollients on the lips, drinking 8 cups of water per day (adding 1-2 teaspoons of lemon juice per 16 ounces will increase salivary flow), avoidance of excess sugar, sucking on sugar free lemon drops or chewing sugarless gum, and maintaining meticulous oral hygiene. Two FDA approved sialogogues can be helpful are cevimeline (Evoxac ®) 30 mg TID and pilocarpine (Salagen ®) 5 mg TID; however, the side effects of sweating, rhinitis, nausea, diarrhea, or visual disturbances may limit their use.

Cheilitis Glandularis

Cheilitis glandularis is a rare inflammatory disease of the minor salivary glands. Patients complain of thick, bumpy lip(s). This disease preferentially affects the lower lip. Cheilitis glandularis tends to preferentially affect light-skinned individuals and males.[77] It mainly affects adults, though case reports in children and adolescents are documented.[78]
Clinically, the lips appear swollen with red, dilated salivary gland orifices that express thick, myxoid saliva onto the vermilion.[79] Submucosal papules and nodules are evident on palpation.[77]

Numerous etiologic causes have been proposed but recently, dysfunction of aquaporin, a membrane protein that plays a role in water and small solute transport and homeostasis,

has been reported.[80] Alteration of water transport may alter salivary composition, leading to changes in the salivary gland environment.[80]

The differential diagnosis includes cheilitis granulomatosa, salivary gland neoplasms, actinic cheilitis or SCC of the lip, or chronic habitual injury. Cheilitis apostematosa profunda is a variant in which the salivary glands express a suppurative discharge.[77]

Lip biopsy helps exclude neoplastic or granulomatous conditions. Characteristic features of cheilitis glandularis include histopathologic findings of chronic sialadenitis and dilated acinar lobules and ducts.[77, 81] In vivo confocal microscopy may also be useful as it has been shown to correlate with the clinical and histopathologic evaluation of cheilitis glandularis.[82]

Treatment includes topical or intralesional corticosteroids or oral antibiotics.[83] Surgical excision of the vermilion may be considered for severe or refractory cases.[83] Patients also must practice sun protection with sun avoidance and sunscreen.

Psoriasis

Oral psoriasis is uncommon. (84-86) Psoriasis, a chronic and well-recognized condition of the skin characterized by erythematous patches or plaques covered by silvery scale, occurs in about 1%-3% of adults.[87] Classic involvement occurs on the scalp, elbows, and knees, though all skin sites can be affected including the nails and genitalia. Intraoral psoriasis is rare even in focused populations with underlying psoriasis.[86]

Intraoral psoriasis and psoriasis of the lips remain a poorly recognized entity particularly in the absence of cutaneous involvement. Case reports and small series suggest that oral psoriasis may appear as migratory erythema, erosions, or pustular plaques, which are similar to geographic tongue/stomatitis. Some, but not all, experts believe that intraoral psoriasis and geographic stomatitis are one and the same condition.[36, 88]

Psoriasis of the vermilion lips presents as nonspecific erythema, scaling, cracking or pustules.[85] There are several clinical presentations including typical scaly erythematous psoriatic plaques that may extend across the vermilion border to the perioral cutaneous skin while also extending to involve the labial mucosa.[36] Psoriasis of the vermilion lips may also present as exfoliative cheilitis and angular cheilitis. Exfoliative cheilitis exhibits diffuse scaling and fissures oriented perpendicular to the vermilion border; this subtype may correlate with the clinical activity of psoriasis vulgaris and pustular psoriasis.[36, 84, 86] Traumatic involvement due to malalignment and malocclusion of the teeth or recurrent traumatic manipulation can exacerbate psoriasis due to the Koebner phenomenon.

The clinical differential diagnosis of psoriasis of the lips includes allergic contact cheilitis, lip licker's dermatitis (Figure 2), lichen planus, lupus erythematosus, candidiasis, Reiter syndrome, and pyostomatitis vegetans. The histologic findings of lip psoriasis are nonspecific and resemble the neutrophilic microabscess and intraepidermal spongiosis of geographic tongue or pyostomatitis vegetans.[85, 88] KOH microscopy and/or

fungal culture may confirm oral candidiasis, however negative KOH microscopy does not exclude a diagnosis of oral candidiasis.

Treatment with mid to high potency topical corticosteroid ointments, such as desonide 0.05% or clobetasol 0.05% ointment, is the treatment of choice in addition to the liberal use of emollients. Clinicians should monitor for the development of acne rosacea, perioral dermatitis, and cutaneous atrophy including telangiectasia and striae with long-term use of topical corticosteroids. Secondary candidiasis or HSV labialis must be considered in the setting of acute exacerbation of symptoms.

Drug associated cheilitis

Drug associated cheilitis is common particularly in the setting of isotretinoin use.[89] Other agents that may cause cheilitis medicamentosa include anticholinergics, antihistamines, antidepressant, antidiuretics, and antihypertensives by the mechanism of xerostomia. Anticonvulsants, antineoplastics, antipsychotics, and narcotics may be associated with lichenoid drug reactions ,phototoxic cheilitis,, erythema multiforme , SJS, or angioedema involving the lips. [38]

NEOPLASTIC CONDITIONS OF THE LIPS

Clinically, inflammation of the vermilion may be difficult to differentiate from premalignant conditions as both may present with erythema with linear lichenoid macules or reticulated plaques at the vermilion. Plaques or patches of white or pale vermilion may represent sun-induced changes that could be associated solar keratosis, dysplasia, or carcinoma. Small 1-3 mm pigmented macules may represent a benign process such as a melanotic macule. Changing color or growth into larger melanotic macules and papules warrant evaluation to exclude melanoma. A biopsy to evaluate these changes is indicated to differentiate inflammatory from premalignant or malignant changes (Table 2).

Actinic Cheilitis

Actinic cheilitis (actinic keratosis of the lip, solar cheilosis) is a premalignant condition associated with chronic exposure to solar/ultraviolet radiation. Actinic cheilitis precedes the development of squamous cell carcinoma of the lip.

Prevalence rates of actinic cheilitis range from 0.5%-2.4% of the population with prevalence rate being substantially higher for populations chronically engaged in outdoor activities.[90, 91] Fair-skinned individuals (Fitzpatrick phototypes I, II) and/or those who work outdoors (i.e. farmers, fisherman, construction workers) are most predisposed but are not exclusively affected. Men are more commonly affected than women. This is hypothesized to be due to increased frequency of outdoor occupations and/or less rigorous sun protection behaviors.[92] Additional risk factors include age (>35 years old), lower socioeconomic status, smoking and genetic predisposition.[90, 93] Solid organ

transplant recipients have a higher prevalence of dysplasia, leukoplakia, and SCC of the lip due to their immunosuppressed status.[94, 95]

Actinic cheilitis may vary from asymptomatic to pain and swelling of the lips and the development of scaly crust on the vermilion. Actinic cheilitis most frequently affects the lower lip as the upper lip is relatively shaded from UV exposure. Diffuse erythema, patchy whiteness, dryness and scaling of the vermilion typify actinic cheilitis. Fissuring, atrophy and loss of the normal lip lines may also be noted. Loss and blurring of the vermilion border is clinically characteristic but may be difficult to discern in elderly patients with associated loss of support structures of the lip. Pain and irritation may be minimal even in the setting of ulceration. Although the appearance of the vermilion may be non-uniform with discrete areas of hyperkeratosis, the presence of induration or ulceration require further evaluation for squamous cell carcinoma. Patients should also be assessed for the presence of cervical lymphadenopathy (unilateral vs. bilateral, mobile vs. fixed) prior to any diagnostic or therapeutic intervention.

The clinical differential diagnosis of actinic cheilitis includes cheilitis glandularis, contact cheilitis, exfoliative/atopic cheilitis, lichen planus, lupus erythematosus, and squamous cell carcinoma. One or more biopsies should be obtained from any area of ulceration, induration, nodularity or hyperkeratosis to exclude malignancy as any single biopsy may not be representative of epithelial dysplasia at non-sampled sites.

The histopathology of actinic cheilitis demonstrates epithelial hyperplasia, parakeratosis, and variable degrees of epithelial dysplasia as well as chronic inflammatory infiltrate, solar elastosis, and vasodilatation. The degree of epithelial dysplasia cannot be predicted by clinical presentation.[96, 97]

Several medical and procedural therapies exist for actinic cheilitis. The need for rigorous sun avoidance and sun protection measures including the regular use of lip sunscreen and broad-brimmed hats should be emphasized. Given the diffuse and premalignant nature of actinic cheilitis, field therapy of the entire lip is recommended rather than focal treatment (Table 4). Topical therapies are indicated for diffuse and mild-moderate actinic cheilitis. However, there are no FDA approved medications for its treatment. For persistent disease with high-grade dysplasia, destructive therapies such as vermilionectomy or laser ablation are indicated.

The prognosis of actinic cheilitis depends on the degree of dysplasia, patient risk factors, and immune status.[94, 95] Actinic cheilitis has been shown to evolve to squamous cell carcinoma in 1.4%-36% of patients over variable time intervals (ranging from 1 to 30 years).[91, 98, 99] Therefore, clinical abnormalities that persist following appropriate treatment of actinic cheilitis warrant further diagnostic evaluation by histopathology.

Squamous cell carcinoma of the lip

Squamous cell carcinoma (SCC) of the lip is the most common oral neoplasm.[94, 100, 101] The lower lip is more commonly affected (89%). [102,101] SCC of the lip presents as

indurated, non-healing red or white papules or ulcers. It is usually asymptomatic and commonly occurs in areas of preexisting actinic cheilitis. (Figure 4) It is associated with chronic UV exposure, tobacco, alcohol exposure, and possibly HPV strains.[94, 100, 101] Organ transplant recipients have a 15-fold increased risk for developing lip cancer due to their immunosuppressed status.[94, 95]

It is more common in fair-skinned Caucasians.[101] Men are more commonly affected than women, though black men are rarely affected. [101] High risk HPV strains may play a role in the development of some lip SCCs, as HPV 16 and 18 are found in 6% of cases; however, these strains are also found in normal oral mucosa.[103] Poor oral hygiene/dentition is associated with worse outcomes in patients with SCC.[104]

Metastases may be present at the time of diagnosis as the lips are a site at high-risk for metastases (8% at time of diagnosis, 14% after 5 years following excision).[100, 105] Lymph node metastases are often on the same side, enlarged, fixed and firm; later stage metastases are to the lung and liver. Staging must be performed at initial examination. The clinician should check for the presence of lymphadenopathy, assess size of the lymph nodes, whether nodes are fixed, and whether they are unilateral as well as signs of distant metastases such as cough, hepatosplenomegaly, or jaundice.

The biologic behavior of lip SCC is related to location and risk factors. Risk of metastasis increases with tumors >2 cm in size, depth of invasion >4 mm, recurrent lesions, perineural invasion, and in patients who are immunosuppressed.[106] Lip cancer is considered to be separate from other oral cancers, of which tongue is the most common and is more likely to be deeply invasive or metastatic.[101]

The differential diagnosis of lip SCC depends on the clinical appearance. For a persistent nodule, neoplastic causes may be considered such as basal cell carcinoma, pyogenic granuloma, amelanotic melanoma, or actinic cheilitis. For a nonhealing ulcer, the differential diagnosis includes, vesiculobullous disorders, oral tuberculosis, syphilis and deep fungal infections.

Proliferative verrucous leukoplakia (PVL) presents initially with innocuous intraoral white plaques; however, PVL is a distinct variant of oral leukoplakia characterized by the progression and expansion of multifocal plaques that develop an exophytic verrucous appearance.[107] Women are significantly more likely to be affected than men (ratio 4:1).[107] Each site/lesion is at high risk for malignant transformation. In contrast to most oral and lip SCC, smoking has not been associated with PVL in most patients.[107] Lip involvement has only rarely been reported. In one case, a patient with PVL was noted to also have involvement of a verrucous plaque on her lower lip, which extended onto the cutaneous surface.[108] Histologic features are variable and range from epithelial dysplasia to verrucousSCC.[107, 108]

The pathophysiology of lip SCC is due to malignant transformation of epithelial cells.[109] On pathology, actinic cheilitis is often found in lip SCC biopsies, suggesting a common etiology and strong relationship between the two.[110,109]

Treatment includes surgical excision with neck dissection for high grade tumors or those with palpable lymph nodes.[111, 112] Radiation therapy has outcomes similar to surgery for lip tumors and is a good option for non-surgical candidates. Radiation therapy, however, does not allow for histologic confirmation.[113] Adjuvant radiation or chemotherapy may be considered for patients with risk of residual disease or perineural invasion.[113]

Conclusions

The lips are highly visible and cosmetically important anatomic structures. Alterations may be distressing and disfiguring. Knowledge of the appropriate examination technique and recognition of normal and abnormal findings is necessary to evaluate the lips, which may display symptoms of systemic disease or pathology. The number of mucocutaneous conditions that affect the lips is quite large and variable. A complete evaluation is necessary in these patients. A careful history and physical examination, associated studies (biopsy, laboratory and microbiology tests), comprehensive review of medications, allergies, and habits all may be helpful. Treatment should be focused on eliminating potential irritant or allergens and treatment of the primary dermatosis.

Tables and Figures

Table 1 Differential Diagnosis of Inflammatory Cheilitis

Common	Rare
Actinic Allergic Atopic Candidiasis Herpes simplex virus infection Irritant (lip lickers, wind burn) Lichen planus Discoid lupus erythematosus Psoriasis Drug-induced EM/SJS Morsicatio labiorum	Amyloidosis Acanthosis nigricans Cheilitis granulomatosa (Miescher's cheilitis) Sarcoidosis Cheilitis glandularis Plasma cell cheilitis Syphilis Exfoliative cheilitis

Table 2 Differential Diagnosis of Lip Neoplasms

Benign	Malignant
Molluscum contagiosum Leukoplakia Verruca Venous lake Labial melanotic macules Lymphangioma Hemangioma	Proliferative verrucous leukoplakia Malignant melanoma Squamous cell carcinoma

Table 3. Contact Cheilitis

Allergic	Irritant
Rare	Very common
T-cell mediated, type IV or delayed hypersensitivity immunologic reaction	Nonspecific inflammatory reaction
Clinical disease occurs 24 to 48 hours after exposure	Environmental factors, sun, cold and wind, lip licking, drooling and pooling of saliva
Precipitating etiology may be obvious or not…	
Pathology → nonspecific or lichenoid; eosinophils	Pathology → nonspecific or lichenoid

Table 4: Treatment of Actinic Cheilitis

Treatment	Advantages	Disadvantages
Topical 5-fluorouracil[114] -5% solution TID x 9-15 days -5% cream BID x 2-4 weeks	Complete healing 2-3 weeks post-treatment	Discomfort, pain, erosions No histologic analysis
Topical diclofenac	Less irritating than topical fluorouracil or imiquimod	Longer treatment times
Topical imiquimod[115]	Persistent clearance after treatment period[116]	Irritation, erythema, induration, erosions, ulceration
Topical imgenol mebutate		Limited data
Photodynamic therapy with methyl/aminolevulinic acid[117, 118]	Good safety profile Better cosmetic outcome	Low complete response rate even with multiple treatments
Liquid nitrogen cryosurgery[119]	Best for localized actinic lesions	No histologic analysis
Electrodessication	Best for localized actinic lesions	No histologic analysis
CO_2 laser vaporization	Normal lip contour, no "significant" scarring	No histologic analysis
Vermilionectomy ("lip shave")[120]	Removes entire vermilion lip Histologic analysis	Paresthesia (25%), pruritus (7.7%), labial scar tension (15.4%), 7.6% labial scar pain[121] Requires specific surgical expertise

Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
BID	Twice daily
CDC	Center for Disease Control
DFA	Direct Fluorescence Antigen
DNA	Deoxyribonucleic Acid
EM	Erythema Multiforme
GI	Gastrointestinal
HIV	Human Immunodeficiency Virus
HMB	Human Melanoma Black
HPV	Human Papillomavirus
HSV	Herpes Simplex Virus
mm	Millimeters
PCR	Polymerase Chain Reaction
QD	Daily
SCC	Squamous Cell Carcinoma
SJS	Stephen-Johnson Syndrome

UV	Ultraviolet
VWS	Van der Woude Syndrome
WHO	World Health Organization
KOH	Potassium Hydroxide

Figure 1 Angular Cheilitis in the setting of Oral Candidiasis (From the collection of Dr. Ginat Mirowski)

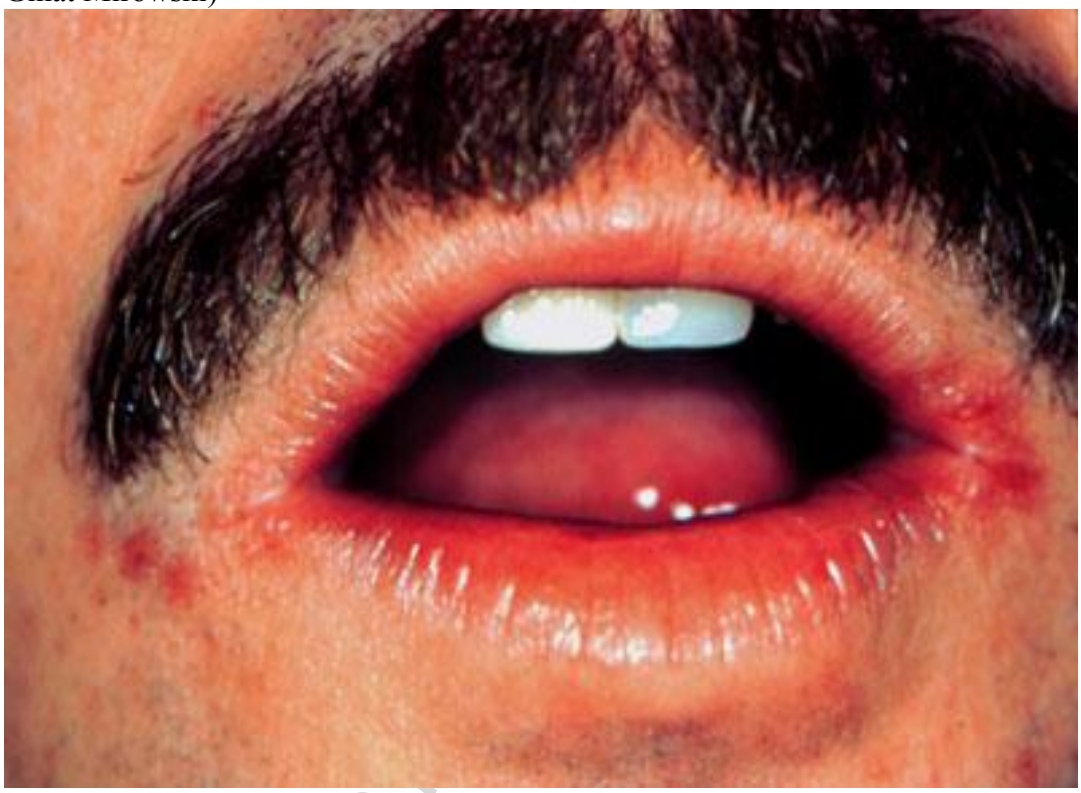


Figure 2 Lip Lickers Cheilitis (From the collection of Dr. Ginat Mirowski)

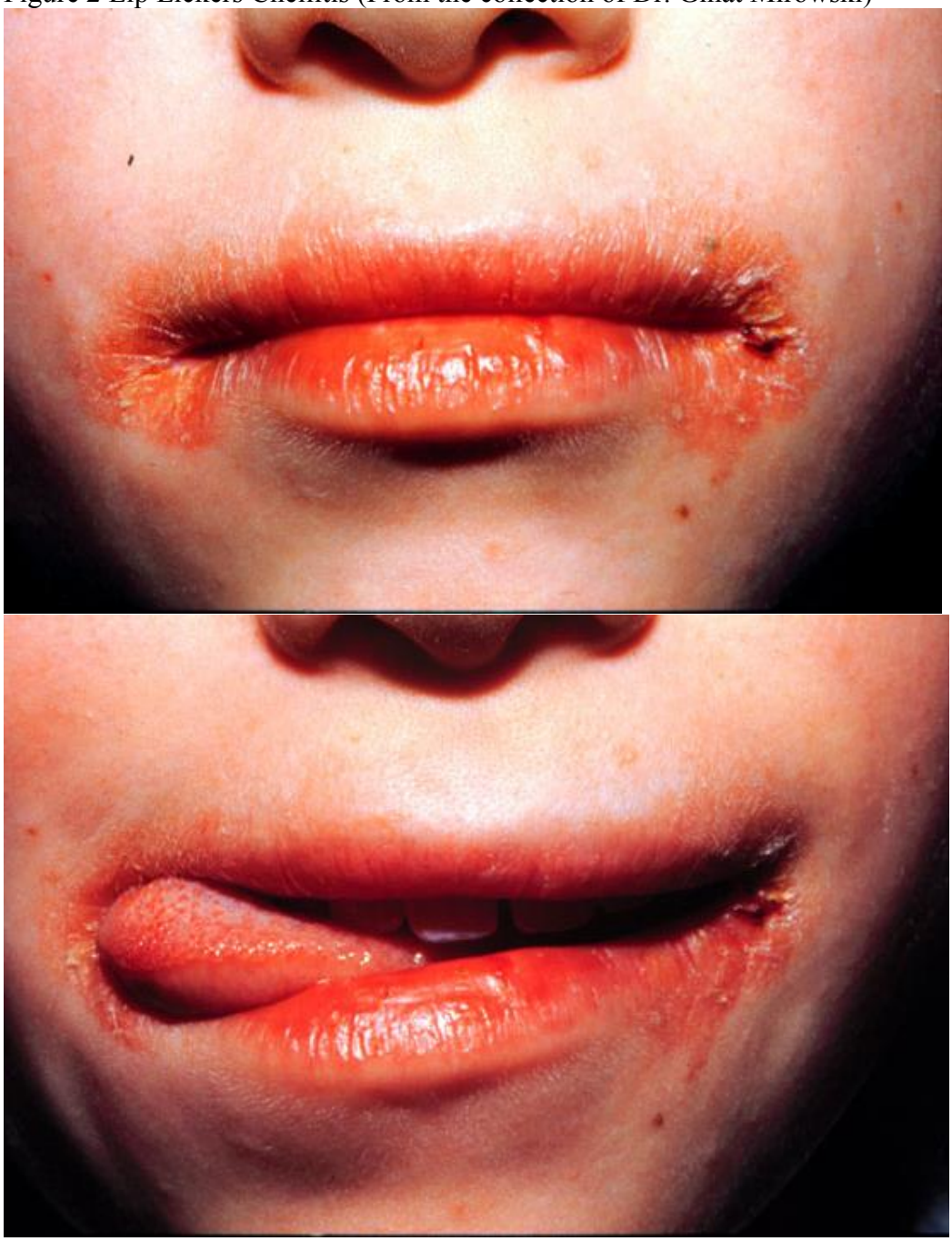


Figure 3 Discoid Lupus Cheilitis (From the collection of Dr. Ginat Mirowski)

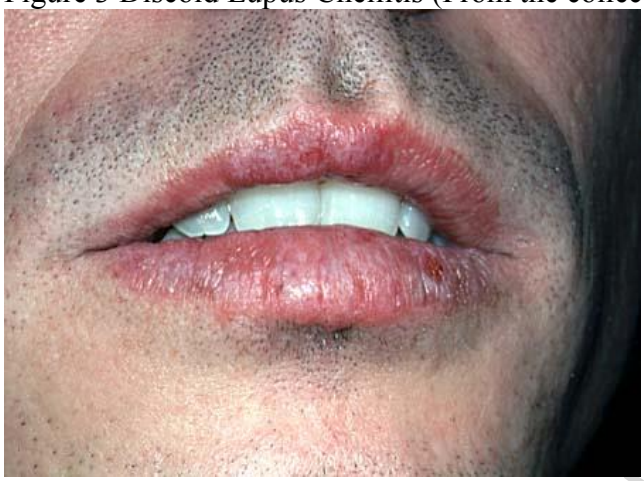
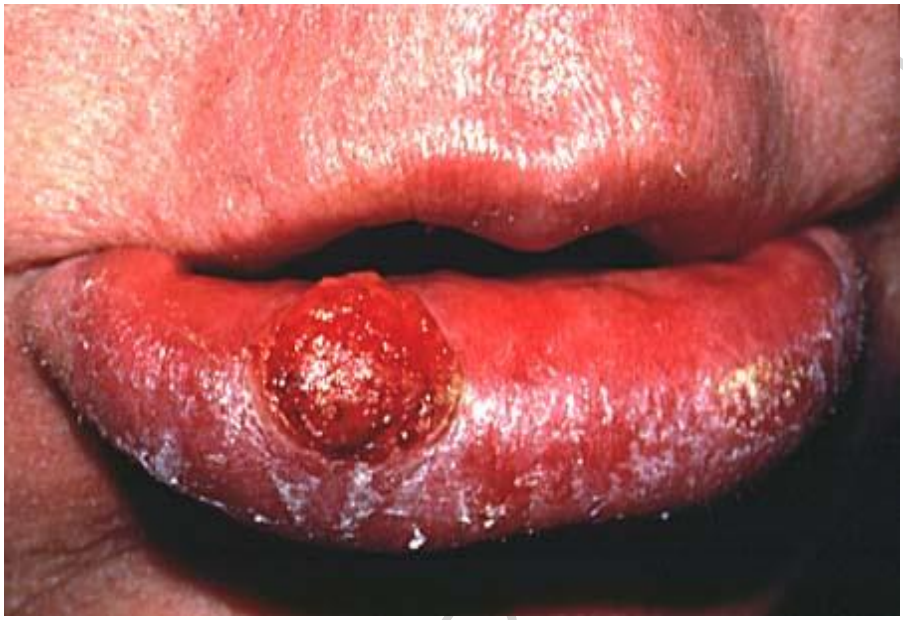


Figure 4 Squamous cell carcinoma in the setting of chronic actinic cheilitis ((From the collection of Indiana University School of Dentistry)



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