Cheilitis. Aphthous ulcer. Premalignant lesions of the oral mucosa. Malignant tumors of the oral mucosa.

Cheilitis Definition

- Cheilitis is a group of oral labial mucosa inflammatory disorders caused by different factors (physical, chemical, infectious, allergic), that can act separately or in combination.

Cheilitis Classification

- Angular Cheilitis
- Simple Cheilitis (congestive, eritematous)
- Glandular Cheilitis
- Keratotic Cheilitis
  - exfoliative cheilitis
  - abrasive cheilitis
- Actinic cheilitis
  - acute actinic cheilitis
  - chronic actinic cheilitis
- Granulomatous Cheilitis

Cheilitis Glandularis

- Cheilitis glandularis (CG) is a clinical diagnosis that refers to an uncommon, poorly understood, and fundamentally benign inflammatory disorder of the submucosal glands in the lower lip. The condition is characterized by progressive enlargement and eversion of the lower labial mucosa that results in obliteration of the mucosal-vermilion interface. With externalization and chronic exposure, the delicate lower labial mucous membrane is secondarily altered by environmental influences, leading to erosion, ulceration, crusting, and, occasionally, infection. Most significantly, susceptibility to actinic damage is increased. Therefore, CG can be considered a potential predisposing factor for the development of actinic cheilitis and squamous cell carcinoma.

Classification

- Historically, the disorder has been subclassified into 3 types: simple, superficial suppurative, and deep suppurative. The deep suppurative type has also been variously referred to as myxadenitis labialis or cheilitis apostematosa, and the superficial suppurative type has been termed Baelz disease. Many believe these subtypes represent a continuum of disease wherein the simple type, if not treated, could become secondarily infected and progress to become the superficially or, eventually, the deeply suppurative type.

History

- CG is a chronic progressive condition. Patients typically present for diagnostic consultation within 3-12 months of onset. Complaints vary according to the nature and the degree of pain, the enlargement and the loss of elasticity of the lip, and the extent of evident surface change.
- Asymptomatic lip swelling initially occurs with clear viscous secretion expressible from dilated ductal openings on the mucosal surface.
- Some patients report periods of relative quiescence interrupted by transient or persistent painful episodes associated with suppurative discharge.
- A burning discomfort or a sensation of rawness referable to the vermilion border may be reported. This is associated with atrophy, speckled leukoplakic change, erosion, or frank ulceration with crusting.

Physical

- CG affects the lower lip almost exclusively. It manifests as progressive, often multinodular enlargement, eversion, and induration.
- Salivary gland duct orifices may be dilated and appear as red or black puncta.
- Viscous clear secretions may initially exit the duct openings spontaneously.
- In more suppurative cases, application of gentle pressure can elicit mucopurulent exudates.
- With advancing lip prominence and mucosal eversion, the mucosal-vermilion junction is obfuscated.
- Prolonged exposure to the external environment results in desiccation and disruption of the labial mucous membrane, predisposing it to inflammatory, infectious, and actinic influences.

CG had historically been subclassified into 3 types, now believed to represent evolving stages in severity of a single progressive disorder.

- In the simple type, multiple, painless, papular surface lesions with central depressions and dilated canals are seen.
- The superficial (suppurative) type (also referred to as Baelz disease) consists of painless, indurated swelling of the lip with shallow ulceration and crusting.
- CG of the deep suppurative type (CG apostematosa, CG suppurativa profunda, myxadenitis labialis) comprises a deep-seated infection with formation of abscesses, sinus tracts and fistulas, and potential for scarring.
- The latter 2 types of CG have the highest association with dysplasia and carcinoma, respectively.

Lab studies

- Microbial culture and sensitivity testing: In cases with acute or chronic suppuration, bacterial culture and sensitivity testing is indicated for selection of appropriate antibiotic therapy.
- Fungal culture or smear: Chronic angular cheilitis or erosive surface changes may be indicative of chronic candidal infection. Confirmation is an indication for appropriate antifungal therapy.
- Lip biopsy is indicated to rule out specific granulomatous diseases that predispose to lip enlargement and to aid in establishing a definitive diagnosis. A representative incisional biopsy specimen should consist of a wedge (or punch) of lip tissue that includes surface epithelium and is of adequate depth to ensure inclusion of several submucosal salivary glands.

Treatment

- For cases attributable to angioedema, administration of an antihistamine may effect temporary reduction in acute nonpurulent swelling.
- Suppurative cases of CG require management with appropriate antimicrobial treatment as determined by culture and sensitivity testing. Concomitant intralesional or oral corticosteroid treatment may potentiate the effectiveness of antimicrobial therapy in cases with nodularity; however, the potential systemic adverse effects of long-term corticosteroid treatment, plus its propensity for promoting local fibrosis and scarring, limit its potential use either as an adjunct to antibiotic treatment or as a single therapeutic modality for CG.
- Topical 5-fluorouracil is useful for treatment of dysplastic actinic cheilitis and to curtail its progression. In conjunction with clinical supervision, it can be prescribed as an alternative to vermilionectomy or as a prophylactic measure following vermilionectomy.

Surgical Care

- In cases where a history of chronic sun exposure exists (especially if the patient is fair skinned or the everted lip surface is chronically eroded, ulcerated, or crusted), biopsy is strongly recommended to rule out actinic cheilitis or carcinoma.
- Surgical excision is not necessary when the diagnosis is actinic cheilitis with atypia or only mild dysplasia; however, patients require ongoing clinical vigilance at regular intervals and instruction in measures to protect the lips from further sun damage.
- Treatment options for cases of actinic cheilitis with moderate-to-severe dysplasia include surgical stripping or vermilionectomy, cryosurgery or laser surgery, or topical chemotherapy with 5-fluorouracil. Given the potential for recurrence and the risk for development of carcinoma, sun protective measures and regular clinical monitoring must be instituted.
- Carcinoma of the vermilion is treated with surgical wedge resection with adequate margins. A palpatory examination of the submental lymph nodes is indicated to rule out regional metastasis.

Cheilitis Granulomatosa (Miescher-Melkersson-Rosenthal Syndrome)

- Granulomatous cheilitis is a chronic swelling of the lip due to granulomatous inflammation. Miescher cheilitis is the term used when the granulomatous changes are confined to the lip. Miescher cheilitis is generally regarded as a monosymptomatic form of the Melkersson-Rosenthal syndrome, although the possibility remains that these may be 2 separate diseases. Melkersson-Rosenthal syndrome is the term used when cheilitis occurs with facial palsy and plicated tongue.
- Melkersson-Rosenthal syndrome is occasionally a manifestation of Crohn disease or orofacial granulomatosis.

History

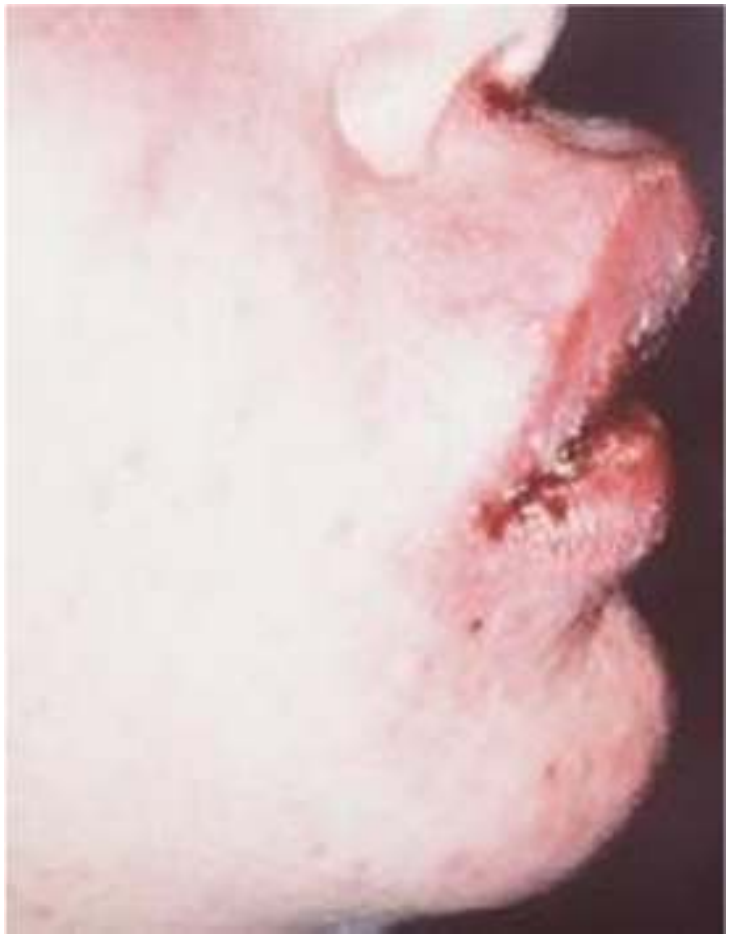
- Cheilitis granulomatosa is episodic with nontender swelling and enlargement of one or both lips. Occasionally, similar swellings involve other areas, including the periocular region.
- The first episode of edema typically subsides completely in hours or days. After recurrent attacks, swelling may persist and slowly increase in degree, eventually becoming permanent. Recurrences can range from days to years.
- Attacks sometimes are accompanied by fever and mild constitutional symptoms (eg, headache, visual disturbance).
- Cranial nerve palsies may be associated. Melkersson-Rosenthal syndrome is the association with facial nerve palsy

Physical

The earliest manifestation is sudden diffuse or occasionally nodular swellings of the lip or the face involving (in decreasing order of frequency) the upper lip, the lower lip, and one or both cheeks. The forehead, the eyelids, or one side of the scalp may be involved (less common). The upper lip is involved slightly more often than the lower lip, and it may feel soft, firm, or nodular on palpation.

Physical

- Once chronicity is established, the enlarged lip appears cracked and fissured with reddish brown discoloration and scaling. The fissured lip becomes painful and eventually acquires the consistency of firm rubber.
- Swelling may regress very slowly after some years.
- Regional lymph nodes are enlarged (usually minimally) in 50% of patients.
- A fissured or plicated tongue is seen in 20-40% of patients.
  - Its presence from birth (in some patients) may indicate a genetic susceptibility.
  - Patients may lose the sense of taste and have decreased salivary gland secretion.
- Facial palsy of the lower motor-neuron type occurs in about 30% of patients.
  - Facial palsy may precede attacks of edema by months or years, but it more commonly develops later.
  - Facial palsy is intermittent at first, but it may become permanent.
  - It can be unilateral or bilateral, partial or complete.
  - Other cranial nerves (eg, olfactory, auditory, glossopharyngeal, hypoglossal) are occasionally affected.



Labial swelling and angular cheilitis.

Lab Studies

- Serum angiotensin-converting enzyme test may be performed to help exclude sarcoidosis.
- Patch tests may be used to help exclude reactions to metals, food additives, or other oral antigens. Some cases may be associated with such sensitivities. If found, avoidance of the implicated allergen is recommended.
- A biopsy of the swollen lip or facial tissues is indicated but only shows lymphoedema and perivascular lymphocytic infiltration during the early stages and later shows granulomas.
- A biopsy may be performed to help exclude Crohn disease and sarcoidosis.

Imaging Studies

- Gastrointestinal tract endoscopy, radiography and biopsy may be used to help exclude Crohn disease.
- Chest radiography or gallium or positron emission tomography (PET) scanning may be performed to help exclude sarcoidosis.
- Panorex dental films may be obtained to assess for the presence of a chronic dental abscess.

Treatment

- Simple compression for several hours daily may produce significant improvement. Intralesional corticosteroids may be helpful in some patients. Success with other treatments has been reported anecdotally. None of the agents listed below has been systematically evaluated.
- Nonsteroidal anti-inflammatory agents
- Antibiotic treatment of dental abscess (resulted in remission in anecdotal cases)
- Mast cell stabilizers
- Clofazimine
- Tetracycline (used for anti-inflammatory activity)
- Methotrexate
- Tacrolimus
- Infliximab

Surgical Care

- Surgery and radiation have been used.
- Surgery alone is relatively unsuccessful.
- Reduction cheiloplasty with intralesional triamcinolone and systemic tetracycline offer the best results. Give corticosteroid injections periodically after surgery to avoid an exaggerated recurrence.

Aphthous Stomatitis

- Recurrent aphthous ulcers (RAUs), or canker sores, are among the most common oral mucosal lesions physicians and dentists observe.
- RAU is a disorder of unknown etiology that causes clinically significant morbidity.
- One to several discrete, shallow, painful ulcers are visible on the unattached mucous membranes. Individual ulcers typically last 1-2 weeks. Large ulcers may last several weeks to months.

Pathophysiology

- RAU is classically divided into 3 clinical forms: RAU minor, RAU major, and herpetiform RAU. RAU affects the following nonkeratinized or poorly keratinized surfaces of the oral mucosa:
  - Labial and buccal mucosa
  - Maxillary and mandibular sulci
  - Unattached gingiva
  - Soft palate
  - Tonsillar fauces
  - Floor of the mouth
  - Ventral surface of the tongue

RAU minor

- RAU minor is the most common form, accounting for 80% of all RAUs. Discrete, painful, shallow, recurrent ulcers measuring 3 mm to smaller than 1 cm in diameter characterize this form. At any time, 1-5 ulcers can be present. RAU minor occurs on the labial and buccal mucosa and on the floor of the mouth. Lesions heal without scarring within 7-10 days.

RAU major

- RAU is formerly known as periadenitis mucosa necrotica recurrens. This form is less common than the others and is characterized by oval ulcers 1-3 cm in diameter. In this relatively severe form, 1-10 major aphthae may be present simultaneously. Ulcers are large and deep, they may coalesce, and they often have a raised and irregular border. On healing, which may take as long as 6 weeks, the ulcers leave extensive scarring, and severe distortion of oral and pharyngeal mucosa may occur. This form most commonly affects the lips, the soft palate, and the fauces.

Herpetiform RAU

- This least common form has the smallest of the aphthae, measuring 1-3 mm in diameter. The aphthae tend to occur in clusters that may consist of tens or hundreds of minute ulcers. Clusters may be small and localized, or they may be distributed throughout the soft mucosa of the oral cavity.

History

- RAUs consist of 1 or several rounded, shallow, punched-out appearing, painful oral ulcers that recur at intervals of a few days to a few months. To evaluate oral ulcers as RAUs, ascertain the following information:
  - Nature of the lesions (number, size, duration, recurrence)
    - The prodromal stage begins with a pricking or burning sensation on the mucosa.
    - The ulcers develop within 24-48 hours.
    - Pain lasts 3-4 days or until a thicker fibrinous cover develops or early epithelialization occurs.
    - Healing is complete in 7-10 days.
  - Age of the patient at onset
  - Cutaneous or mucosal changes
  - Symptoms of other organ system involvement
  - Current medications

Host factors associated with RAU

- Genetic - Family history evident in some cases
- Hematinic deficiency - Iron, folic acid, or vitamin B-12 deficiencies possible
- Immune dysregulation - Possible role
- Stress - Physical or emotional stress often reported by patients as associated with recurrent outbreaks

Environmental factors associated with RAU

- Local, chemical, or physical trauma may initiate ulcer development in patients who are susceptible (pathergy).
- Allergy may stimulate an outbreak.
- The role of microbial infection is debated.

HIV infection (associated with lesions)

- Aphthouslike oral ulcerations involving all 3 types of RAUs are observed. About 66% of patients who are HIV positive have herpetiform and major RAUs.
- Ulcerations must be distinguished from those caused by HIV medications and fungal, viral, or bacterial infections.

Behçet syndrome (associated with lesions)

- This complex, multisystemic inflammatory disorder of unknown cause is characterized by recurrent oral aphthae and at least 2 of the following findings: genital aphthae, synovitis, cutaneous pustular vasculitis, posterior uveitis, or meningoencephalitis.
- Oral aphthae of Behçet syndrome are similar to those in RAUs, though they are more extensive and frequent.
- The incidence is highest in Japan, Southeast Asia, the Middle East, and southern Europe and in persons aged 30-40 years.
- Behçet syndrome is strongly associated with human leukocyte antigen B51 (HLA-B51).

Gluten-sensitive enteropathy

- Less than 5% of patients with RAUs have gluten-sensitive enteropathy (GSE), also known as celiac disease, or other minor mucosal abnormalities of the small intestine.
- Bowel symptoms may not be present, but patients may have folate deficiency, and they sometimes have reticulin antibodies.

Physical

- Regardless of the clinical form of RAU, ulcers are confined to the nonkeratinized mucosa of the mouth, sparing the dorsum of the tongue, the attached gingiva, and the hard palate mucosae that are keratinized. Although patients often have submandibular lymphadenopathy, fever is rare. Most patients are otherwise well.

RAU minor

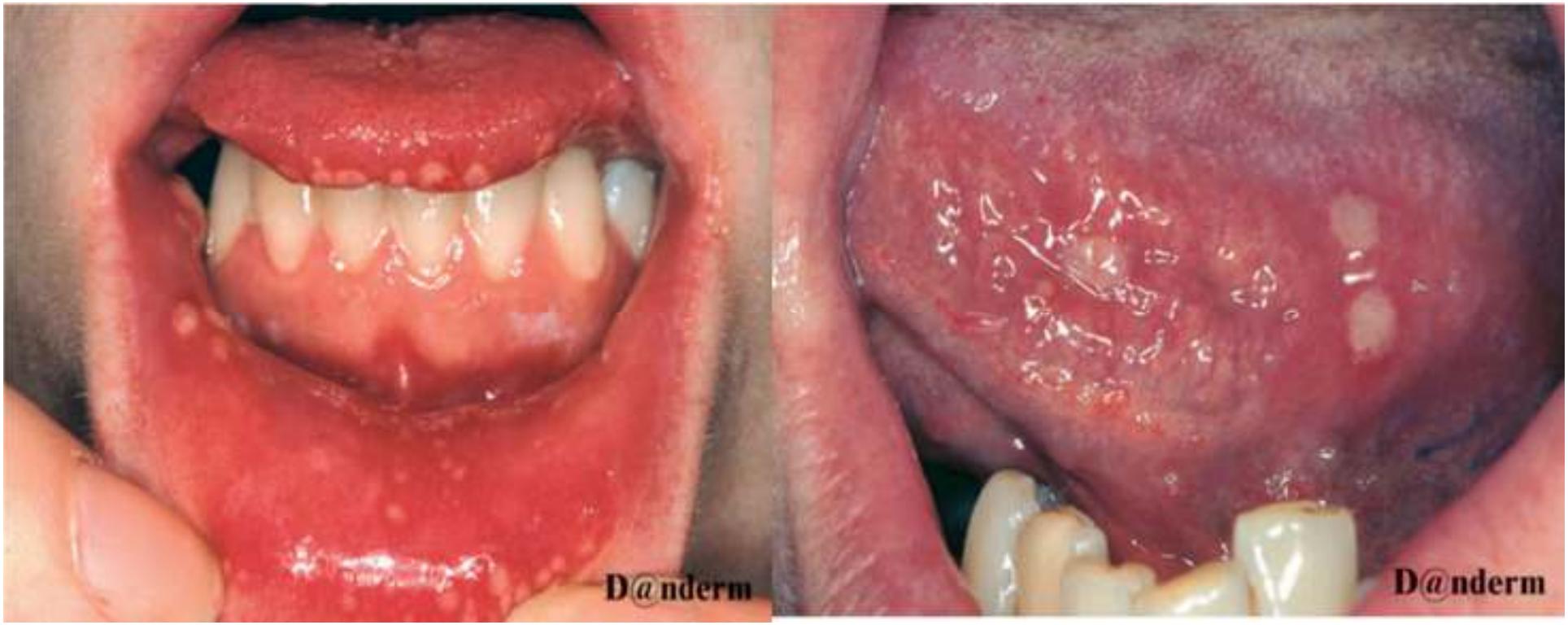
- RAU minor is characterized by 1-5 discrete, shallow ulcers smaller than 1 cm in diameter.
- The ulcers are covered by a yellow-gray pseudomembrane (fibrinous exudate) and are surrounded by an erythematous halo.

RAU major

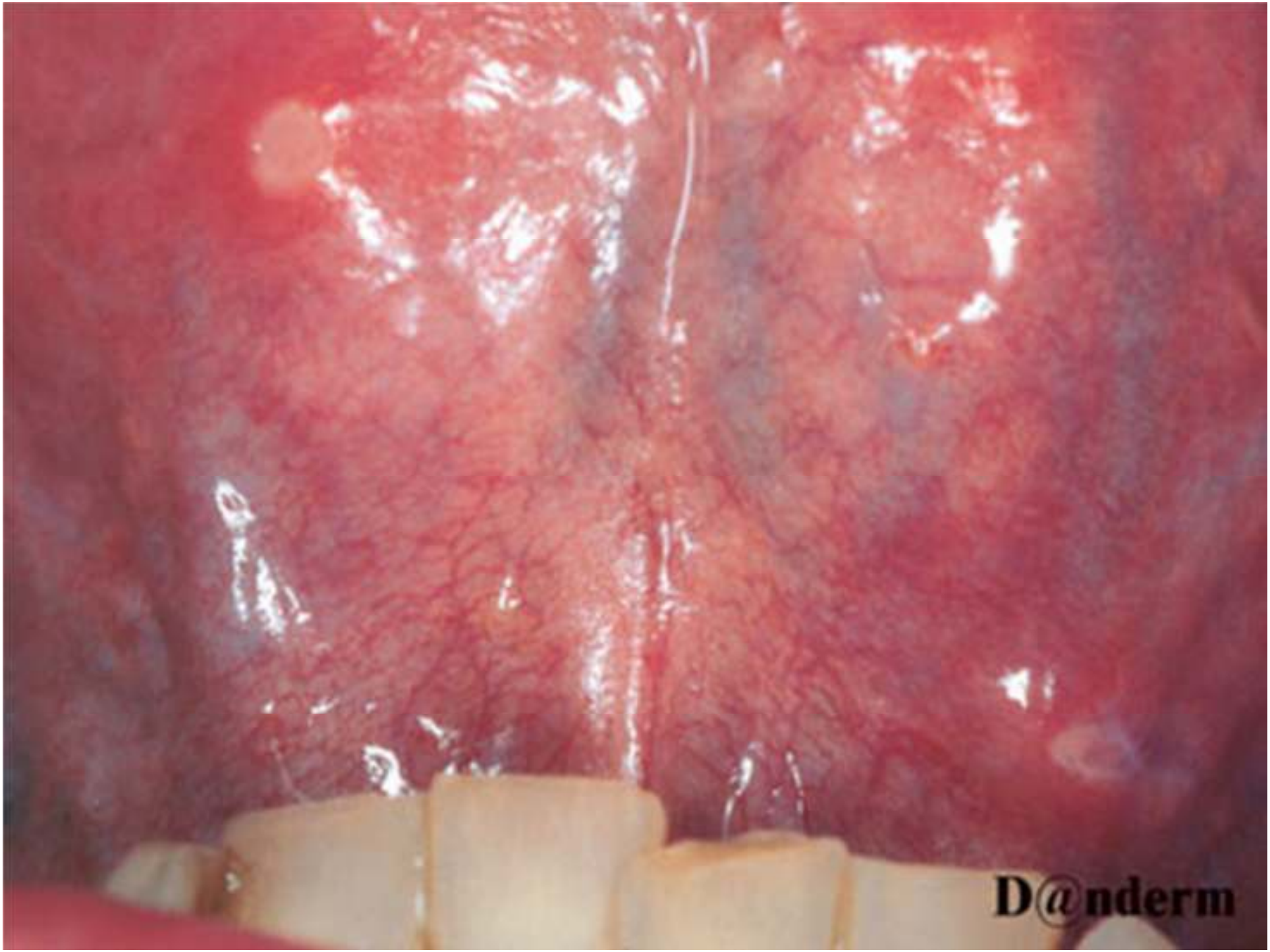
- RAU major is characterized by oval ulcers that are larger (1-3 cm in diameter) and deeper than those observed in RAU minor.
- The ulcers may coalesce and often have a raised, irregular border.

Herpetiform RAU

- Herpetiform RAU is characterized by crops of smaller ulcers measuring 3 mm in diameter, with sometimes more than 100 lesions present at 1 time.
- The ulcers can coalesce to produce a widespread area of irregular ulceration.



Aphthous stomatitis


D@nderm

Lab Studies

- CBC determination
- Measurement of erythrocyte sedimentation rate (ESR)
- Determination of iron, ferritin, folate, and vitamin B-12 levels
- Potassium hydroxide (KOH) examination of the lesion
- Tzanck smears, viral cultures, or even skin biopsy to exclude HSV

Other Tests

- The following procedures may be indicated if other disease is suspected:
  - Colonoscopy
  - Biopsy with hematoxylin-eosin stains and cultures
- Swab the ulcer to obtain material for a polymerase chain reaction to identify *H pylori* DNA.

Medical Care

- RAUs are treated by using a variety of agents for palliative, prophylactic, and curative purposes. Many of the treatments are used without substantial research demonstrating therapeutic results.
- Therapy for RAU must be directed by the extent of the condition, as determined by the patient and the clinician. Patients often complain of great pain when clinical examination reveals only a minor ulcer of 1-2 mm in diameter. In addition, the frequency and the extent of involvement should direct therapy.

Topical regimens

- Anti-inflammatory (eg, corticosteroids) and immunomodulatory agents (eg, retinoids, cyclosporin) are used initially.
  - Topical gels
  - Creams
  - Pastes
  - Ointments
  - Sprays
  - Rinses

Adjuvant rinses limit inflammatory effect and reduce bacterial counts

- Chlorhexidine gluconate
- Betadine, tetracycline, and dilute salt water rinses
- Dilute hydrogen peroxide
- Topical lidocaine or benzocaine

Systemic agents

- Colchicine 0.6 mg 3 times a day (tid)
- Cimetidine 200 mg 2 or 4 times a day (bid/qid)
- Azathioprine (Imuran) 50 mg per day (qd)
- Thalidomide (This is the only treatment the US Food and Drug Administration [FDA] had approved for the treatment of major aphthae in individuals with HIV infection.)
- Multivitamins with iron are recommended but do not have any clear benefit.

Diet

- An elimination diet may help control outbreaks by revealing allergic stimuli that stimulate oral lesions.
- A gluten-free diet helps patients with GSE (celiac disease) control outbreaks of aphthae.
- Patients with oral lesions should adhere to a diet of soft foods.
- Advise avoidance of salt and spices to prevent unnecessary aphthae irritation. Some patients report aphthae after exposure to English walnuts or pineapple. In such cases, remission may be achieved by avoiding the inciting agent.

Leukoplakia, Oral

- The World Health Organization first defined oral leukoplakia as a white patch or plaque that could not be characterized clinically or pathologically as any other disease; therefore, lichen planus, candidiasis, and white sponge nevus were excluded. At the 1983 international seminar, the current definition was composed:
- Leukoplakia is a whitish patch or plaque that cannot be characterized clinically or pathologically as any other disease, and is not associated with any physical or chemical causative agent, except the use of tobacco.
- Oral white lesions include leukoplakias (as defined above), keratoses, leukoplakias of clear infective origin (candidal, syphilitic, hairy leukoplakia associated with Epstein-Barr virus), candidosis, lichen planus, oral submucous fibrosis, lupus erythematosus, dyskeratosis congenita, and frank carcinomas.

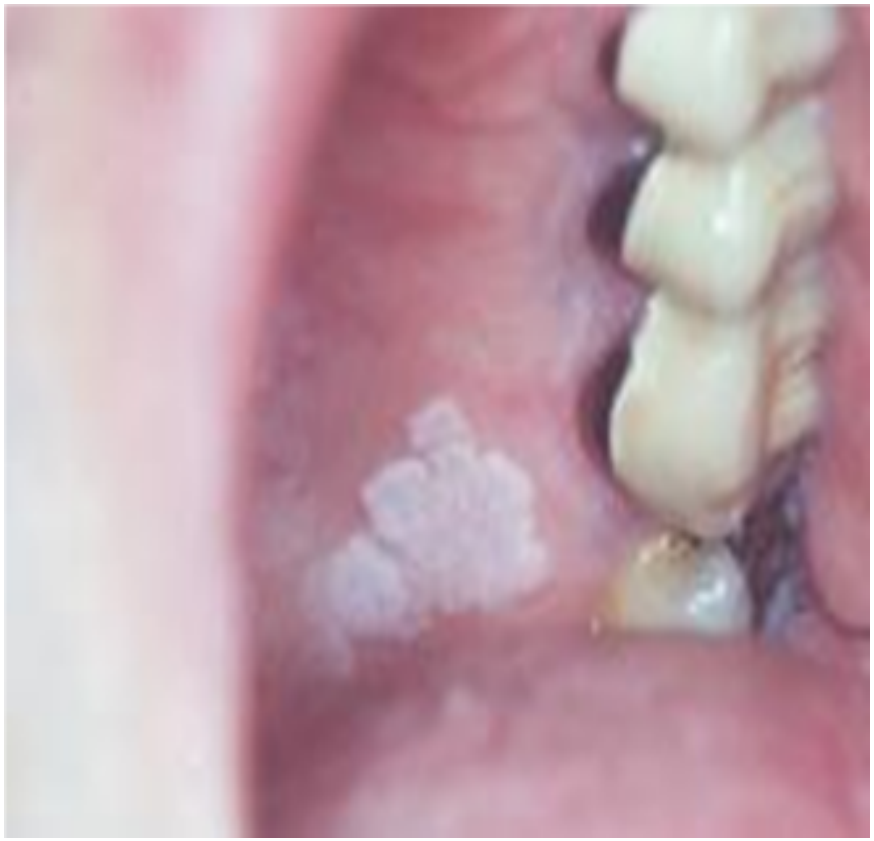
Pathophysiology

- No etiologic factor can be identified for most persistent oral white plaques
- Patients with idiopathic leukoplakia have the highest risk of developing cancer. In studies of these patients, 4-17% had malignant transformation of the lesions in less than 20 years. The risk of developing malignancies at lesion sites is 5 times greater in patients with leukoplakia than in patients without leukoplakia.
- Dysplastic lesions do not have any specific clinical appearance; however, where erythroplakia is present, dysplasia is likely.
- Dysplasia is evident in 17-25% of biopsy samples of leukoplakias.

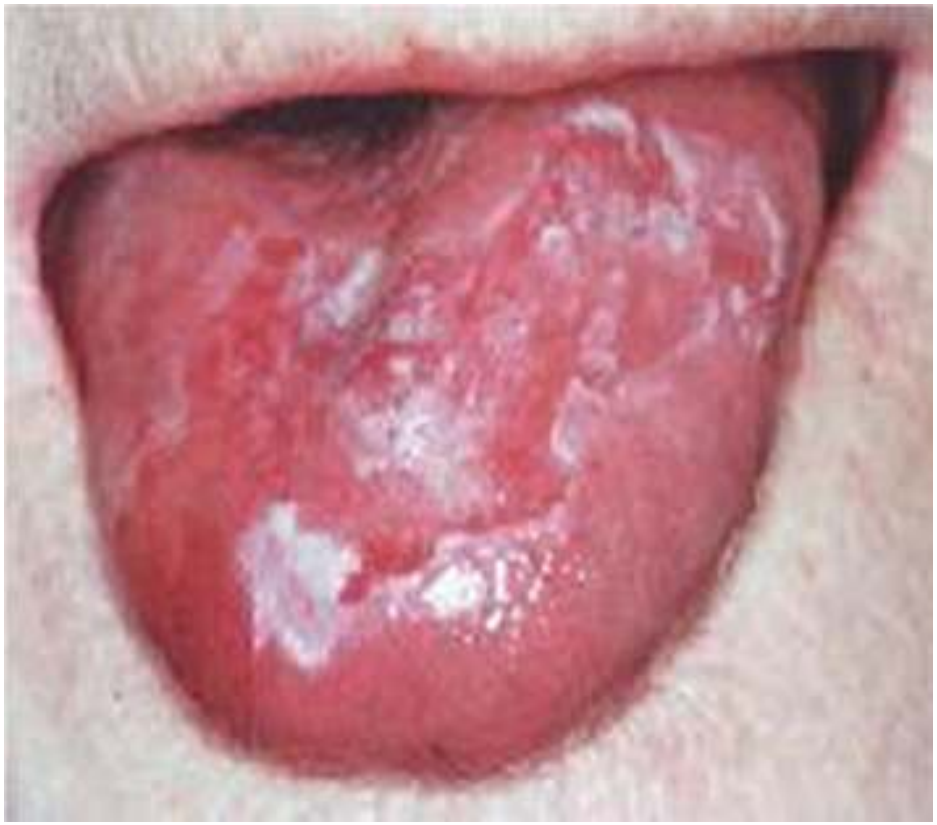
Physical

- Leukoplakias are white lesions that cannot be removed with a gauze swab.
- Most leukoplakias are smooth, white plaques (homogeneous leukoplakias).
- Most leukoplakias occur on the lip, the buccal mucosae, or the gingivae.
- Some leukoplakias are white and warty (verrucous leukoplakia).
- Some leukoplakias are mixed white and red lesions (erythroleukoplakias or speckled leukoplakias).
- Dysplastic lesions do not have any specific clinical appearance; however, where erythroplasia is present, dysplasia, carcinoma in situ, and frank carcinomas are more likely to be seen.
  - The site of the lesion is relevant; leukoplakias on the floor of the mouth or on the ventrum of the tongue and the lip are sinister.
  - The size of the lesion appears to be irrelevant. Even small dysplastic lesions may lead to multiple carcinomas and a fatal outcome.

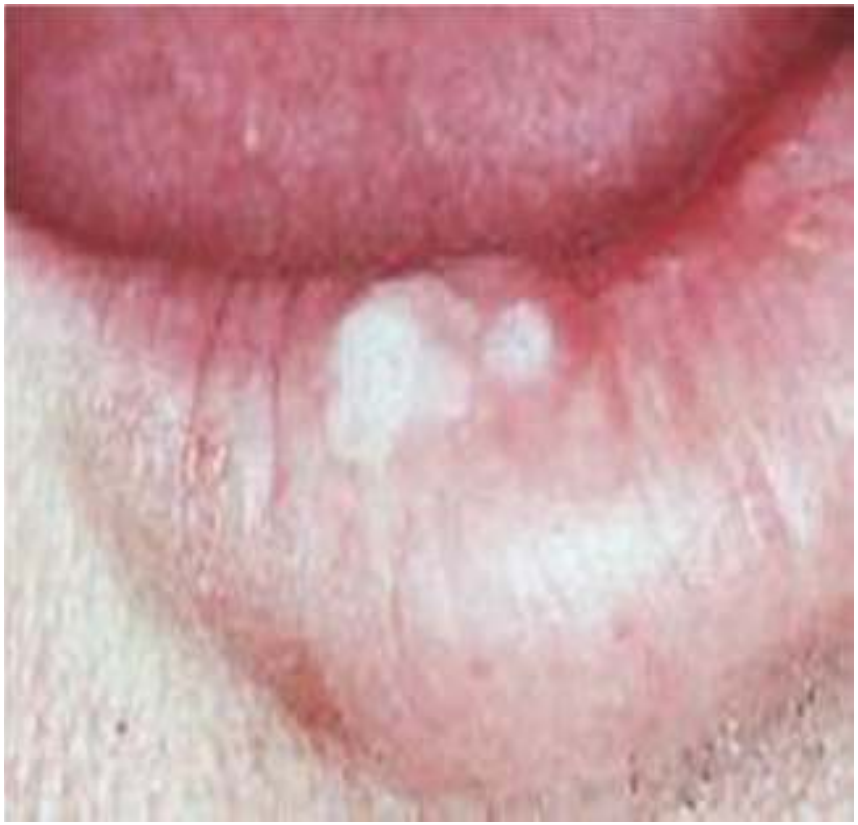
Homogeneous leukoplakia.



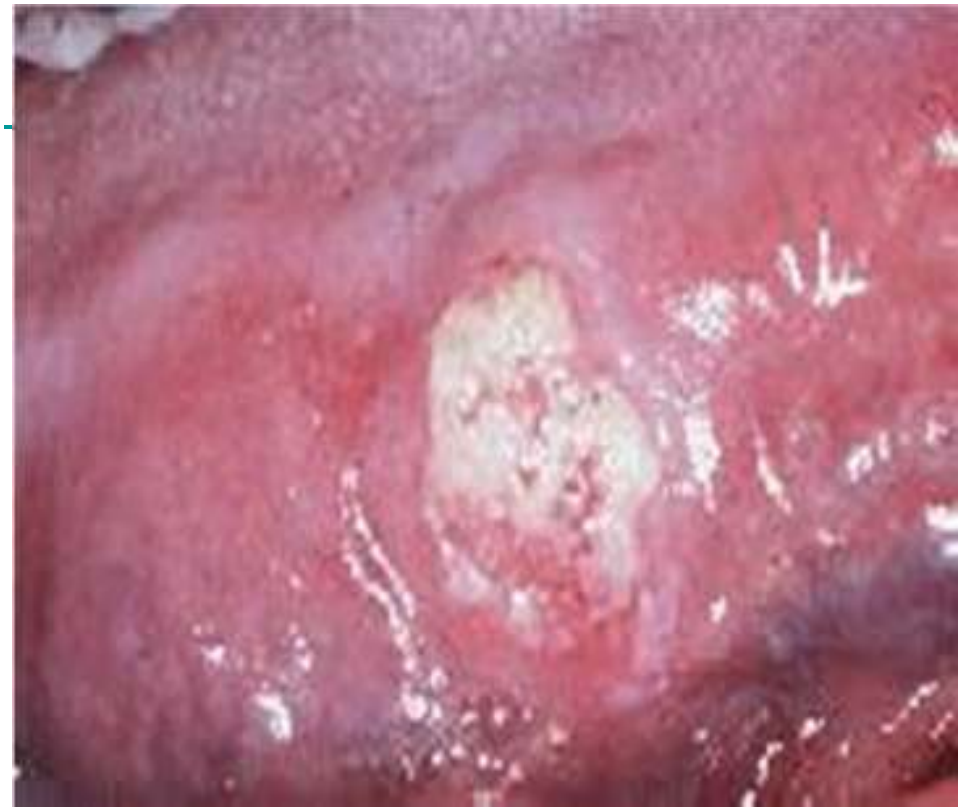
Erythroleukoplakia.



Verrucous or nodular leukoplakia.



Carcinoma referred to as a leukoplakia.



Causes

- No etiologic factor can be identified for most persistent oral leukoplakias (idiopathic leukoplakia).
- Known causes of leukoplakia include the following:
  - Trauma (eg, chronic trauma from a sharp or broken tooth or from mastication may cause keratosis)
  - Tobacco use: Chewing tobacco is probably worse than smoking.
  - Alcohol
  - Infections (eg, candidosis, syphilis, Epstein-Barr virus infection): Epstein-Barr virus infection causes a separate and distinct non–premalignant lesion termed hairy leukoplakia.
  - Chemicals (eg, sanguinaria)
  - Immune defects: Leukoplakias appear to be more common in transplant patients.

Oral biopsy

- The recently introduced, computer-assisted, oral brush biopsy is a detection tool providing evidence of cellular abnormalities in precancerous and cancerous lesions. With the aid of a highly specialized, neural, network-based, image-processing system specifically designed to detect oral epithelial precancerous and cancerous cells, the pathologist can detect as few as 1 or 2 abnormal individual cells in several hundred thousand cells.
- The detection of 1 or 2 such abnormal cells is sufficient to warrant a histologic specimen obtained by scalpel biopsy.

Histologic Findings

- The histopathologic features are highly variable, ranging from hyperkeratosis and hyperplasia to atrophy and severe dysplasia. The histologic assessment of oral epithelial dysplasia is notoriously unreliable. Many studies show interpathologist and intrapathologist variation in diagnosing dysplasia. Clearly, molecular studies are indicated to introduce more objectivity. Studies of p53 and other molecular markers, loss of heterozygosity, and DNA ploidy as molecular markers are currently underway.
- Besides the fact that the criteria for diagnosing dysplasia are ill defined, another serious problem exists. A tissue specimen from a biopsy may not be representative of the whole lesion.

Medical Care

- The objective of care is to detect and to prevent malignant change. The presence of the white plaque alone does not require treatment.
- Several management regimens have been suggested; however, no large trials have shown a definitive, reliable treatment. No evidence base exists on which to reliably recommend treatment. Indeed, current evidence suggests that no treatment is of reliable benefit.
- Possible courses of action include the following:
  - Wait and watch
  - Medical therapies (eg, anti-inflammatory agents, vitamins, cytotoxic agents)
  - Surgical removal (eg, scalpel, laser, cryoprobe, electrosurgery, photodynamic therapy)
- Patients should avoid any causal factor, such as use of tobacco and alcohol. Leukoplakias can regress under these circumstances.
- Any degree of dysplasia in a lesion at a high-risk site must be taken seriously and the lesion should be removed.
- Occasionally, patients are treated by photodynamic therapy or topical cytotoxic agents.
- Patients should be examined regularly, probably at 3- to 6-month intervals.

Retionoids

Retinoids are currently being investigated as a possible treatment modality. They appear to be very effective but can have severe adverse effects on liver function and may cause teratogenicity. Their beneficial effect appears to last only during the treatment.

Surgical Care

Management of leukoplakias is far from satisfactory, and no large trials offer guidance as to the most reliable treatment. Surgical removal of leukoplakia seems one reasonable option. Some experts surgically remove these lesions with scalpel, laser, or cryoprobe. Laser excision is preferred to fulguration. Others point out the possible aggravation of dysplasia caused by such operative intervention and that surgical removal of aneuploidic lesions does not improve mortality rates.

Cancers of the Oral Mucosa

- Approximately 90% of oral cancers are squamous cell carcinoma (SCC), which is seen in older men, typically on the lip or lateral part of the tongue.
- Oral SCC (OSCC) is particularly common in the developing world. The etiology appears to be multifactorial and strongly related to lifestyle, mostly habits and diet (particularly tobacco alone or in betel, and alcohol use), although other factors, such as infective agents, also are implicated. Immune defects, defects of carcinogen metabolism, or defects in DNA-repair enzymes underlie some cases. Sunlight exposure predisposes to lip cancer.
- Findings from the history and clinical examination by a trained diagnostician are the primary indicators of OSCC, but the diagnosis must be confirmed histologically.

Pathophysiology

- In OSCC, modern DNA technology, especially allelic imbalance (loss of heterozygosity) studies, have identified chromosomal changes suggestive of the involvement of tumor suppressor genes (TSGs), particularly in chromosomes 3, 9, 11, and 17. Functional TSGs seem to assist growth control, while their mutation can unbridle these control mechanisms.

Pathophysiology

- Carcinogen-metabolizing enzymes are implicated in some patients. Alcohol dehydrogenase oxidizes ethanol to acetaldehyde, which is cytotoxic and results in the production of free radicals and DNA hydroxylated bases; alcohol dehydrogenase type 3 genotypes appear predisposed to OSCC.
- Cytochrome P450 can activate many environmental procarcinogens. Ethanol is also metabolized to some extent by cytochrome P450 IIEI (CYP2E1) to acetaldehyde. Mutations in some TSGs may be related to cytochrome P450 genotypes and predispose to OSCC.
- Glutathione S transferase (GST) genotypes may have impaired activity; for example, the null genotype of GSTM1 has a decreased capacity to detoxify tobacco carcinogens. Some GSTM1 and GSTP1 polymorphic genotypes and GSTM1 and GSTT1 null genotypes have been shown to predispose to OSCC.
- *N*-acetyltransferases NAT1 and NAT2 acetylate procarcinogens. *N*-acetyl transferase NAT1*10 genotypes may be a genetic determinant of OSCC, at least in some populations.

Pathophysiology

- Tobacco is a potent risk factor for oral cancer. An interaction occurs between redox-active metals in saliva and the low reactive free radicals in cigarette smoke. The result may be that saliva loses its antioxidant capacity and instead becomes a potent pro-oxidant milieu.

History

- Some OSCCs arise in apparently normal mucosa, but many are preceded by clinically obvious premalignant lesions, especially erythroplakia (red patch), leukoplakia (white patch), a speckled leukoplakia (red and white patch), or verrucous leukoplakia, and many others are associated with such lesions (especially in Southeast Asia).

History

- Erythroplastic lesions are velvety red plaques, which in at least 85% of cases, show frank malignancy or severe dysplasia. In contrast, most white lesions are not malignant or premalignant. Speckled or verrucous leukoplakias are more likely to be premalignant. Carcinomas are seen 17 times more frequently in erythroplakias than in leukoplakias, but leukoplakias are far more common. The prevalence of malignant transformation in leukoplakias ranges from 3-33% over 10 years; homogeneous leukoplakias are only very occasionally premalignant, but speckled or verrucous leukoplakias are more likely to be premalignant.

OSCC may manifest as the following:

- A red lesion (erythroplakia)
- A granular ulcer with fissuring or raised exophytic margins
- A white or mixed white and red lesion
- A lump sometimes with abnormal supplying blood vessels
- An indurated lump/ulcer (ie, a firm infiltration beneath the mucosa)
- A nonhealing extraction socket
- A lesion fixed to deeper tissues or to overlying skin or mucosa
- Cervical lymph node enlargement, especially if hardness is present in a lymph node or fixation: Enlarged nodes in a patient with oral carcinoma may be caused by infection, reactive hyperplasia secondary to the tumor, or metastatic disease. Occasionally, a lymph node is detected in the absence of any obvious primary tumor.

Physical

- A systematic and thorough examination of the mouth, fauces, and cervical lymph nodes should be performed by a clinician trained in the diagnosis of oral diseases, and a general physical examination is indicated. Dental practitioners and dental care professionals are trained in the examination of the mouth.
- Advanced caries, periodontal disease, or periapical lesions may need early attention, especially if radiotherapy is to be used in management of a tumor. Examine the teeth, periodontium, and entire mucosa in good lighting.

Physical

- The most common sites of oral cancer include the lower lip, the lateral margin of the tongue, and the floor of the mouth; however, all areas should be scrutinized. The sump area or "coffin corner" at the posterior tongue/floor of the mouth is a common site for cancer but may be missed by cursory inspection; special care is needed to ensure close examination.
- The clinical appearance of oral cancer is highly variable and includes ulcers, red or white areas, lumps, or fissures.
- Lesions always must be palpated after inspection to detect induration and fixation to deeper tissues.

Erythroplasia

- Erythroplasia (erythroplakia) is a red and often velvety lesion, which, unlike leukoplakias, does not form a plaque but is level with or depressed below the surrounding mucosa.
- Of erythroplasia lesions, 75-90% prove to be carcinoma or carcinoma in situ or show severe dysplasia.
- Erythroplasia affects patients of either sex in their sixth and seventh decades and typically involves the floor of the mouth, the ventrum of the tongue, or the soft palate.
- Red oral lesions usually are more dangerous than white oral lesions.

Oral mucosal white patches

- Oral mucosal white patches usually result from increased keratinization or candidosis.
- Currently, the term leukoplakia is usually restricted to white patches for which a cause cannot be established; therefore, the term implies a diagnosis by exclusion (eg, lichen planus, candidiasis).
- The term leukoplakia is also used irrespective of the presence or absence of epithelial dysplasia. Leukoplakia is a clinical term for a persistent adherent white patch with no histologic connotation and no implied premalignant potential; keratosis is the term now commonly used. Oral carcinoma can also appear as a white patch.

Physical

- Most lip cancers manifest on the lower lip at the mucocutaneous junction as a chronic small lump, ulcer, or scabbed lesion.
- Most intraoral cancers manifest on the middle third of the lateral margins of the tongue with an erythroplastic component and, sometimes, induration.
- Late tongue cancer may manifest as an exophytic lesion, an ulcer, or an area of superficial ulceration with induration.
- A typical malignant ulcer is hard with heaped-up and often everted or rolled edges and a granular floor.
- The floor of the mouth is the second most common intraoral site for cancer and more commonly is associated with leukoplakia. Most cancer arises in the anterior floor of the mouth as an indurated mass that soon ulcerates, resulting in slurring of speech.

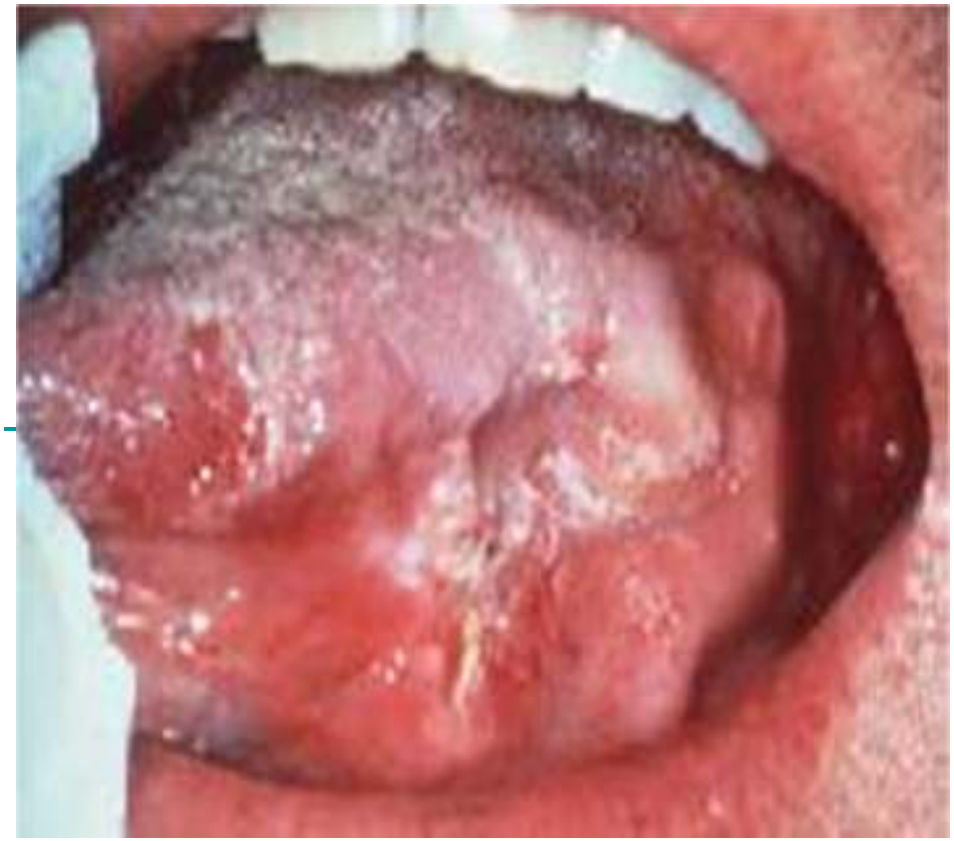
Physical

- Carcinomas of the alveolus or gingiva are mostly seen in the mandibular premolar and molar regions, usually as a lump (epulis) or ulcer. The underlying alveolar bone is invaded in 50% of cases, even in the absence of radiographic changes, and adjacent teeth may be loose.
- Carcinomas of the buccal mucosa are mostly seen at the commissure or in the retromolar area. Most are ulcerated lumps, and some arise in candidal leukoplakias.

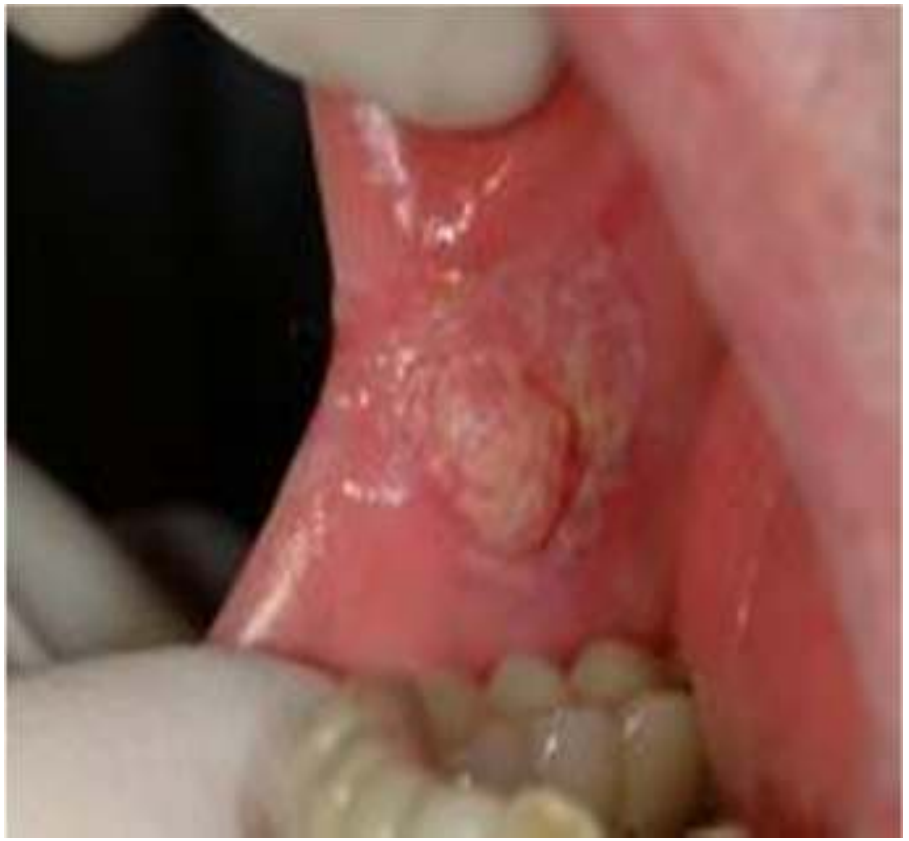
Physical

- Lymph node examination is of paramount importance, and general examination and, possibly, endoscopy, may be indicated to detect metastases
- From 30-80% of patients with oral cancer have metastases in the cervical lymph nodes at presentation.
- Oral cancer predominantly metastasizes locally and to regional lymph nodes, primarily in the anterior neck. Later, dissemination to the lungs, liver, or bones may occur.
- Any chronic oral lesion should be regarded with suspicion, especially when found in an older patient, when lesions appear, with induration, with fixation to underlying tissues, with any recent changes in appearance, with associated lymphadenopathy, or with no obvious explanation for the lesion.
- Examine the entire mucosa because widespread dysplastic mucosa (field change) or a second neoplasm may be present.
- Carefully record the location of suspicious lesions, preferably on a standard topographic diagram.

Oral squamous cell carcinoma in the most common intraoral site manifesting as a chronic, indurated ulcer.



Early oral squamous cell carcinoma in the buccal mucosa arising from a chronic candidal leukoplakia in a person who smokes heavily. The lesion was a painless, chronic indurated lump.



Lab Studies

- The principles are to confirm the diagnosis histopathologically and to determine whether malignant disease is present elsewhere, including the following:
- Bone, muscle, or primary tumors: Other primary tumors are typically located in the upper aerodigestive tract (eg, mouth, nares, pharynx, larynx, esophagus). Whether endoscopy is warranted to detect such tumors in all cases remains controversial.
- Metastases: This initially occurs to regional lymph nodes and later to the liver, bones, and brain. Imaging studies may help detect abnormalities missed during the clinical examination.

Blood tests include the following:

- Liver function tests: Results may reveal metastases in persons with advanced disease.
- Complete blood cell count and hemoglobin value
- Urea and electrolyte measurements
- Blood group testing and cross-matching
- Calcium level: As many as 4% of patients with cancer in the head and neck may have elevated serum calcium levels. This is a poor prognostic indicator primarily found in persons with advanced disease.
- Serum ferritin, alpha-antitrypsin, and alpha-antiglycoprotein levels: Persons with high-stage cancer of the head and neck also have increased levels of serum ferritin, alpha-antitrypsin, and alpha-antiglycoprotein, while those at any stage of disease have increased haptoglobin levels (although not known if this is true specifically for oral cancer). Additionally, prealbumin levels are decreased slightly in persons at any stage. Results from assays of these serum constituents cannot be regarded as sufficiently specific or sensitive to be of reliable clinical value, and this, unfortunately, is also true of the many tissue markers thus far described.

Imaging Studies

- Photography
- Chest radiography
- Jaw radiography
- Other imaging investigations include MRI or CT scanning of the primary site, of the head and neck, and of suspected sites of lymph node or distant metastases. Sentinel node biopsy, MRI, 18-fluorodeoxyglucose positron emission tomography (FDG-PET) scanning, or ultrasonography of the neck (or combinations) can be used to delineate the extent of cervical node metastasis.

Incisional biopsy

- Incisional biopsy, guided when appropriate by vital staining, is essential to confirm the diagnosis. A biopsy must be performed on any oral mucosal lesion suggestive of cancer, including any ulcer that does not heal within 2-3 weeks.
- An incisional biopsy is always required, usually with the patient under local anesthesia.
- Always take a biopsy specimen of the red lesions if both red and white lesions are present because red, rather than white, areas are more likely to show dysplasia.
- In vivo staining may help if difficultly arises when deciding which area is most appropriate for the biopsy, particularly if widespread lesions are present.
- Staining with toluidine blue followed by a rinse with 1% acetic acid and then saline may stain the areas most suggestive of findings and indicate which need a biopsy. Oral carcinoma in situ and early invasive carcinoma have an affinity for toluidine blue dye, and although several false-positive results may be encountered, these can be minimized by restaining after 14 days. Toluidine blue clearly is more effective in experienced hands and when used with appropriate clinical judgment.

Incisional biopsy

- Counterstaining with Lugol iodine solution may enhance the usefulness of toluidine blue staining.
- Various light sources are becoming available to help delineate areas for biopsy.
- The biopsy specimen should be sufficiently large to include enough suspect and apparently normal tissue to provide the pathologist an opportunity to make the diagnosis and to not have to request an additional specimen. Most patients tolerate (physically and psychologically) one biopsy session. Most biopsy wounds, whether 0.5 cm (too small) or 1.5 cm long (usually adequate), heal within 7-10 days; therefore, taking at least one ample specimen is better than having to repeat the procedure. Some clinicians always take several biopsy specimens at the first visit to avoid the delay, anxiety, and aggravation resulting from a negative pathology report for a patient in whom cancer is strongly suspected.
- Fix biopsies in 10% normal saline to prevent autolysis.

Excisional biopsy:

- Avoid excisional biopsies unless the lesion is small because the procedure is unlikely to have achieved excision of an adequately wide margin of tissue if the lesion is malignant but will have destroyed clinical evidence of the site and character of the lesion for the surgeon or radiotherapist. This can be avoided by tattooing the site.

Lymph node biopsy

- A biopsy is best performed on regional lymph nodes suggestive of cancer using a fine-bore needle to aspirate cells for cytologic examination. Ultrasound-guided fine-needle aspiration cytology is now favored.
- False-negative results are possible, but the primary danger of incisional biopsy is that it may seed malignant cells.
- In practical terms, ipsilateral, firm or hard, enlarged regional lymph nodes in a patient with an obvious oral carcinoma are likely to include metastases.

Histologic Findings

- The epithelium forms islands resembling normal stratified squamous epithelium, except that the islands are invading the underlying tissues and undergoing aberrant keratinization. Instead of the keratin being formed and shed from the surface, it is formed within the substance of an epithelial island, producing a keratin whorl or epithelial pearl. This is a feature of well-differentiated carcinoma.
- Epithelial islands may be discrete and circumscribed, although they are invading the underlying tissues quite extensively or appear more moth eaten with loss of basement membrane; however, loss of basement membrane is not a prerequisite of an invasive tumor. Occasionally, an endogenous foreign body giant cell reaction to the keratin from ruptured pearls occurs.
- SCC consists of small islands of squamous cells with a high mitotic index and nuclear hyperchromatism but no obvious keratinization.
- Poorly differentiated SCC consists of sheets of cells showing extreme pleomorphism, giant nuclei, and multiple and bizarre mitoses and often is difficult to distinguish from other malignancies, particularly poorly differentiated lymphoma or melanoma. In this instance, immunocytochemical markers such as keratins, common leukocyte antigen, and melanoma-specific antibodies are indicated.

Staging Classification

1993 American Joint Committee on Cancer

TNM classification for Oral Cancers

- Primary tumor
  - T0 - No primary tumor
  - Tis - Carcinoma in situ
  - T1 - Tumor 2 cm or smaller
  - T2 - Tumor 4 cm or smaller
  - T3 - Tumor larger than 4 cm
  - T4 - Tumor larger than 4 cm and deep invasion to muscle, bone, or deep structures (eg, antrum)
- Lymphatic node involvement
  - N0 - No nodes
  - N1 - Single homolateral node smaller than 3 cm
  - N2 - Nodes(s) homolateral smaller than 6 cm
  - N3 - Nodes(s) larger than 6 cm and/or bilateral
- Tumor metastasis
  - M0 - No metastasis
  - M1 - Metastasis noted

Staging

- Stage I - T1, N0, M0
- Stage II - T2, N0, M0
- Stage III
  - T3, N0, M0
  - T1, T2, T3, N1, M0
- Stage IV
  - T4, N0, M0
  - Any T, N2 or N3, M0
  - Any T, any N, any M

Medical Care

- Combined clinics that include surgeons, oncologists, and support staff usually have an agreed treatment policy and offer the best outcomes. OSCC currently is treated largely by surgery and/or irradiation, although few unequivocal controlled trials of treatment modalities have been conducted. Photodynamic and chemotherapy have occasional applications.
- Important factors to consider are quality of life and patient education. In one study, at least 6 months after the diagnosis of oral cancer, 47% of participants still smoked and 36% drank alcohol to excess. Only one third of the participants were aware that these habits were important in the development of oral cancer.
- The prognosis of OSCC is site dependent. For intraoral carcinoma, the 5-year survival rate may be as low as 30% for posterior lesions presenting late, as they often do. For lip carcinoma, the 5-year survival rate often is more than 70%.

Radiotherapy

- Advantages of radiotherapy include the facts that normal anatomy and function are maintained, general anesthesia is not needed, and salvage surgery is available if radiotherapy fails.
- Disadvantages mainly include the facts that adverse effects are common; cure is uncommon, especially for large tumors; and subsequent surgery is more difficult and hazardous and survival is reduced further.
- Radiotherapy can be performed by external beam radiation (teletherapy), which is commonly accompanied by adverse effects, or interstitial therapy (eg, brachytherapy, plesiotherapy). Implants of iridium Ir 192 for a few days are often used, supplying a radiation dose equivalent to teletherapy but one that is confined to the lesion and immediate area.

Surgical Care

- The goal of surgery is to remove the primary tumor together with a margin of clinically normal tissue to ensure complete excision of malignant tissue. Surgery thus provides a one-stage definitive procedure, from which the patient normally recovers within 10-14 days. Although modern reconstructive techniques can produce good orofacial aesthetics and function, neither can be totally ensured.
- Surgery provides complete tumor and lymph node excision. A full histologic examination can then be performed for staging purposes and to help predict prognosis and the need for adjuvant radiotherapy. Surgery also provides another option of treatment for radiotherapy-resistant tumors.
- Disadvantages primarily are perioperative mortality and morbidity, but modern techniques have significantly decreased these risks, as well as the aesthetic and functional defects. When OSCC is fatal, it almost always is either because of failure to control the primary tumor or because of nodal metastases. Death resulting from distant metastasis is unusual.

Pharmacotherapy

The goals of pharmacotherapy are to reduce morbidity associated with secondary infection and to prevent complications:

- *Antiviral agents*
- *Antibiotics*
- *Antifungal agents*