EAOM Handbook

FIRST EDITION

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A collection of brief reviews based on sound scientific data, prepared by EAOM members

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ATYPICAL & IDIOPATHIC FACIAL PAIN

Definition

According to the International Association for the Study of Pain (IASP), chronic facial pain refers to symptoms which have been present for at least 6 months. 'Atypical' pain is a diagnosis of exclusion after other conditions have been considered and eliminated (i.e. it is idiopathic) and is characterized by chronic, constant pain in the absence of any apparent cause in the face or brain. Many information sources suggest that all 'unexplained' facial pains are termed Atypical Facial Pain but this is not the case. Categories of idiopathic facial pain conditions include Neuropathic Pain due to sensory nerve damage, Chronic Regional Pain Syndrome (CRPS) from sympathetic nerve damage and Atypical Facial Pain.

Atypical odontalgia, or phantom tooth pain is a variation of atypical facial pain where intense discomfort is centered around a tooth or group of teeth with no obvious dental or oral disease.

Epidemiology

Atypical facial pain is more common in women than in men; most patients attending a facial pain clinic are women aged between 30 and 50 years. Although any area of the face can be involved, the most commonly affected area is the maxillary region. In the majority of patients there is no disease or other cause found. In a few patients the symptoms represent serious disease. In a small number of patients the pain may be one consequence of significant psychological or psychiatric disease.

Clinical presentation

Atypical facial pain is very variable in its presentation. Often it is characterized by continuous, daily pain of variable intensity. Typically, the pain is deep and poorly localized, is described as dull and aching, and does not waken the patient from sleep. At onset the pain may be confined to a limited area on one side of the face, while later it may spread to involve a larger area.

Neuropathic pain is a constant ache or burning feeling localized to one area in the head and neck and is due to dysfunction of the sensory nerve supply to that area of tissue.

CRPS pain is often similar in character but with some change in intensity from day to day. The part of the face affected is often much more diffuse than with Neuropathic pain as the

sympathetic nerves each supply a much wider area than the normal sensory nerves. In CRPS the patient will usually report a feeling of swelling of the painful tissue and often reddening of the overlying skin.

Atypical odontalgia is characterized by continuous, dull, aching, or burning pain of moderate intensity in apparently normal teeth or endodontically treated teeth and occasionally in extraction sites. Atypical odontalgia is not usually affected by testing the tooth and surrounding tissues with cold, heat or electric stimuli. Moreover, the toothache characteristics frequently remain unchanged for months or years, contributing to the differentiation of atypical odontalgia from pulpal dental pain. Occasionally, the pain may spread to adjacent teeth, especially after extraction of the painful tooth.

Aetiopathogenesis

The lack of a demonstrable organic cause and the high prevalence of anxiety and depression among patients with idiopathic facial pain have led to the hypothesis that the condition is of psychogenic origin. However, the psychological profile of these patients is similar to that of other chronic pain patients and it possible that their psychological distress constitutes a consequence rather than a cause of their pain. Genetic factors may be important in some patients developing chronic facial pain as their nerves are susceptible to damage from minor insults that would not produce chronic pain in a 'normal' patient. This can be seen in patients where protracted pain follows a successful minor procedure such as a tooth extraction.

Diagnosis

There are no specific tests that can confirm the diagnosis of idiopathic facial pain. A thorough clinical assessment must be carried out by an experienced clinician to eliminate other possible causes of pain, such as infections of the sinuses or teeth, undetected cancerous lesions and muscle-based pain. Neurological examination of the head and neck is always necessary, and an ENT assessment or imaging studies of the face and brain may be needed in some patients. In the case of atypical odontalgia, tooth vitality tests and radiographic examination will be needed to exclude dental disease.

Often the diagnosis will change over time as the clinical findings change and stabilize. Many patients only get a final diagnosis quite late in the course of their disease as pain conditions do not always give patients 'typical' symptoms. This does not reflect a lack of

competence in the clinician. In some cases the response of the symptoms to certain drug treatments may help focus the diagnosis.

Treatment

Idiopathic facial pain is managed by a variety of methods including drugs, psychological treatments and physical treatments such as acupuncture and TENS nerve stimulation. However some patients have a poor response to all treatments, which is as disappointing for the clinician as the patient. Many patients have had consultations with a variety of specialists, multiple ineffective treatments, and often surgical explorations that have perplexed the symptoms and diagnosis.

Management of the patient is better achieved through a multidisciplinary approach intended to improve patient's quality of life as well as relieving the pain. This involves reducing the disability caused by the pain often with an increase in mood, activity and social contact. Medical management of idiopathic facial pain is mainly through the use of tricyclic antidepressant and anticonvulsant drugs. Though developed for use in the treatment of depression or epilepsy, these medicines have proved very helpful in large numbers of patients. The tricyclic antidepressants such as amitriptyline and nortryptyline are often generally helpful in both reducing pain experience and improving mood and coping and are often the core drug treatment. More recently developed antidepressant drugs such as fluoxetine and paroxetime seem less effective. Newer antiepileptic medication such as gabapentin and valproate are very successful in treating neuropathic pain, where they are the initial drugs of choice. Education, physical therapy, psychological counseling, and alternative pain management strategies, such as acupuncture and biofeedback, may also be useful in the holistic approach to patient care. Surgical procedures are rarely effective and can aggravate the condition and may lead to a painful facial numbness called anaesthesia dolorosa.

Atypical odontalgia patients may undergo many unsuccessful dental procedures before the diagnosis is made. Once the diagnosis is made, dental treatment aimed to relieve the pain is best avoided since it can result in further deterioration of the patient's dentition without any beneficial effect on the pain. Gabapentin or similar drugs, combined with tricyclic antidepressants can make the extremes of the pain less severe but must be used continuously, not only during an acutely painful episode.

Prognosis and complication

In some patients, modern drug treatment can completely eliminate the pain. However the treatments, whether medical, psychological or physical, more commonly only reduce the intensity of symptoms and the consequent pain-related disability. In many patients the pain in some form will remain lifelong. The pain syndromes themselves rarely lead to any life-threatening complications although in severe cases severe depression must be assessed. However, complications can follow multiple invasive treatments in an effort to abolish the pain, particularly destructive surgical procedures on nerves, which should be avoided.

Prevention

Adequate local anaesthesia during surgical procedures and good postoperative pain control may be useful in preventing sensitization of the central nervous system pain pathways and the onset of chronic pain. This is also true in patients with shingles (zoster), where appropriate antiviral and corticosteroid treatment at the time of the shingles rash can prevent nerve damage and neuropathic pain (post-herpetic neuralgia).

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BEHÇET´S SYNDROME

Definition

Behçet´s Syndrome is an inflammatory disorder, now considered as a systemic vasculitis of uncertain aetiology, characterised by a very wide spectrum of clinical features and by unpredictable exacerbations and remissions.

This condition was first recognised in ancient Greece by Hippocrates in the 5th century BC. The condition was later described by the Greek ophthalmologist Benedict Adamantiades (1931), and six years later by the Turkish dermatologist Hulusi Behçet. As a result some authors prefer the term “Adamantiades-Behçet Syndrome”. However, it was Behçet who also described the classical clinical triad of oral and genital ulceration with ocular inflammation.

The main manifestations of Behçet´s disease are recurrent oral and genital ulceration, eye problems and skin lesions. However, nearly all organs and systems can be affected by this widespread vasculitis, and hence the features of this condition may be multiple and varied.

Epidemiology

Behçet´s Syndrome occurs throughout the world with varying prevalence. It is uncommon in Western Europe and the USA (from 0.1 to 7.5 patients per 100.000 inhabitants), while being more prevalent in the Mediterranean Countries, South East Asia (2-20/100.000), in the so-called “silk route” countries (13-370/100.000) and particularly in countries such as Japan (13-30/100.000) and Turkey (80-370/100.000). There is also an increased prevalence in certain ethnic groups, while the prevalence of the disease is also dependent on the geographic area of their residence.

Onset of disease can occur at any age, but is typically in the third decade of life. The clinical picture may take some time to develop but is usually complete in a mean of 15 months from the time of onset. Few neonatal cases have been reported, and children are rarely affected. Young patients have the same presentation, while early onset and male gender are associated with more severe disease. Both genders are equally affected, although large series of patients in certain Mediterranean countries and the Middle East showed that there is a male predominance (1.5-5:1). Familial occurrence has been reported in 1 to 18% percent of patients, mostly of Turkish, Israeli and Korean origin.

Clinical presentation

The multiple manifestations of Behçet´s Syndrome have been traditionally divided into major features (oral ulceration, genital ulceration, inflammatory eye disease and skin lesions) and minor (arthritis, neurological involvement, peripheral arterial and venous disease, gastrointestinal and pulmonary or renal involvement), based on their frequency and not on their clinical severity. The relative frequency of these manifestations varies geographically.

Recurrent oral ulceration is the most common feature of Behçet´s Syndrome (95-100%). Clinically the oral lesions are similar to those that may be observed in patients with Recurrent Aphthous Stomatitis and may be also classified into minor, major or herpetiform. Minor ulcers (< 1 cm.) are rounded or oval, shallow, covered by whitish or greyish pseudomembrane and surrounded by an erythematous halo. Major ulcers are larger (>1 cm.), deeper, more painful and heal more slowly, often with scarring. Herpetiform ulcers are uncommon, more numerous (from 10 to 100) and smaller (1-2 mm.) although lesions may occasionally become confluent and form larger lesions.

Genital ulcers (57-93%) are painful and morphologically similar to oral lesions. The most frequently involved sites are the scrotum and penis in males and the labia in females. Deep ulcers may cause discomfort in sitting down and walking or cause dysuria or dyspareunia and usually heal with scarring.

Ocular lesions (30-90%) occur in the uvea and retina. Lesions are usually bilateral, although the severity may be asymmetrical. Patients usually present within the first 2 or 3 years of the onset of the disease and may experience sudden attacks of visual loss, blurred vision and associated eye pain. Isolated anterior uveitis and hypopyon are not infrequent and are relatively benign lesions. Severe ocular complications may present including retinal detachment, glaucoma, cataract or blindness.

Skin lesions (38-99%) can be divided into two main types, erythema nodosum-like lesions and papulopustular or acneiform lesions. Both types can occur in either gender with erythema nodosum-like lesions more frequent in female patients and usually occurs on the front of the legs. These lesions are painful and resolve spontaneously leaving deeply pigmented areas and sometimes ulceration. Papulopustular or acneiform lesions are more common in male patients and are usually found on the back, face and neck and should be differentiated from adolescent acne.

The primary lesion in Behçet´s Syndrome is vasculitis and vessels of all kind and size may be affected. Peripheral arterial and venous disease may cause embolization, occlusion and pseudoaneurysms.

Generally, arthropathy (16-84%) in Behçet´s patients shows a non-erosive, non-deforming and oligoarticular or monoarticular pattern.

Different vasculitis-related neurological, gastrointestinal, cardiovascular and pleuropulmonary lesions may be observed in Behçet´s patients. Some of them may lead to serious complications.

Aetiopathogenesis

At present, Behçet´s Syndrome cannot be classified as a hereditary disease nor as an infectious disease or an autoimmune disorder, and is best described as a multifactorial condition arising from a combination of endogenous and exogenous factors. Familial cases (1-18%) are relatively uncommon and Behçet´s Syndrome does not follow a Mendelian pattern. It is therefore difficult to attribute the aetiopathogenesis to genetic factors alone.

Susceptibility to Behçet´s Syndrome is strongly associated with the Human Leukocyte Antigen HLA-B51, particularly in patients from Japan, Mediterranean and Middle Eastern Countries. HLA-B51 is more common in males than in females and is also associated with ophthalmic and more severe disease. Other HLA antigens have shown interesting relations with this condition. Thus, HLA-B27 is closely related to arthritic lesions and HLA-B12 to mucocutaneous lesions. Current research in this area includes investigation into new genetic factors and markers (HLA-DRw8 or HLA-B15, variants of ICAM-1 gene or MIC-A gene and many others) and to understand the role they play.

Overall the evidence of an infectious cause is still inconclusive. There is some evidence that microbial infections may trigger cross-reactive autoimmune responses, leading to overt Behçet´s Syndrome. Interestingly Behçet suggested a viral aetiology in his original publication. Several studies have identified herpes simplex virus type 1 (HSV1) DNA in peripheral blood lymphocytes and monocytes or serum antibodies to HSV1 in a high proportion in Behçet´s patients, but not in a proportion statistically significant in biopsy samples from oral ulcers. *In vitro* studies suggest that a possible hypersensitivity to certain *Streptococcus sanguis* antigens may play a part in the pathogenesis.

The presence of increased levels of circulating IgG immune complexes, particularly during symptomatic periods, but without deposition observed in biopsy samples from lesions, decreased lymphocytes T helper (T4) / T suppresor (T8) ratio, decreased activity of NK cells or increased levels of interleukin IL-10, and IL-2 have been reported in several studies. However, there is no definitive consensus about how these findings are linked to the pathogenesis.

Diagnosis

There are no specific laboratory tests to confirm the diagnosis of Behçet´s Syndrome.

In the absence of a significant pathognomonic finding, the diagnosis of Behçet´s Syndrome depends entirely on careful history-taking and clinical findings. Different international classification criteria have been developed to ensure comparability of groups of patients for research and to provide greater objectivity to the diagnosis. The guidelines proposed by International Study Group for Behçet´s Disease are the most commonly used for research purposes. These criteria require recurrent oral ulceration as an essential symptom, plus two or more of the following symptoms: recurrent genital ulceration, ocular lesions, skin lesions or positive pathergy test (table 1). Despite the numerous diagnostic criteria published, problems still arise as features may not be present at the same time and incomplete forms of the condition may occur.
The differential diagnosis of Behçet´s Syndrome includes recurrent aphthous stomatitis, viral infections, Reiter´s Syndrome, Stevens-Johnson´s Syndrome, inflammatory bowel disease, PFAPA Syndome, MAGIC Syndrome, Sweet´s Syndrome, sarcoidosis, multiple sclerosis, and HLA-B27 related syndromes such as ankylosing spondylitis.
The pathergy test is performed by piercing a sterile 20-gauge needle subcutaneously into the forearm, without injection of saline. It is considered as positive when the puncture leaves an aseptic erythematous nodule or pustule larger than 2 mm. in diameter after 24 or 48 hours. At one time the pathergy test was thought to be diagnostic, but has been shown to be unreliable in terms of both its specificity and its geographical variability. Indeed only 20-60% of Behçet´s patients present positive pathergy tests.

Treatment

In the absence of understanding of the aetiopathogenesis an d knowledge of a curative therapy, the management of these patients is directed at the control of the symptoms and to suppress the inflammatory vasculitis. There is no established standard therapeutic regimen due to the variability of clinical manifestations of each individual patient. The choice of the treatment depends on the clinical features and is best managed by a multidisciplinary team.
Oral ulcers are treated in a similar way as those that recurrent aphthous stomatitis patients present. Generally, the less severe cases are treated with topical corticosteroids such as triamcinolone acetonide (0.05-0.5%), betamethasone (0.05-01%) or clobetasol propionate (0.05%) in ointments or in mouthwashes. Prednisone (5 mg./20ml. of water) or sucralfate suspensions mouthwashes or topical administration of Amlexanox (5%) are other treatment possibilities. Severe cases are treated by the systemic administration of immunomodulatory drugs (colchicine, prednisone,

azathioprine, ciclosporin, mycophenolate mofetil, tacrolimus, thalidomide, dapsone, pentoxifylline, methotrexate, cyclophosphamide or interferon-alpha) administered by appropriately qualified clinicians and in such a way as to minimise the risk of unwanted secondary effects.
Genital and skin lesions must be kept clean to avoid contaminated secondary infection. There are usually managed with topical corticosteroids or corticosteroids in combination with antibiotics. Lesions at multiple sites may require systemic therapy.
The treatment of ocular lesions requires careful consideration in collaboration with an ophthalmologist. Colchicine, topical mydriatics and corticosteroids are prescribed for the treatment and prevention of anterior uveitis. Acute posterior uveitis attacks are treated using high doses of corticosteroids or ciclosporin. In certain cases other immunomodulating medications may be required.
The treatment of other manifestations of this syndrome is based on the usage of different combinations of anti-inflammatory analgesics, corticosteroids and immunosuppressive agents and even surgical intervention if appropriate. Therapeutic priority is given to the treatment of vital organ lesions.

Prognosis and complications

Behçet´s Syndrome runs a chronic course with unpredictable exacerbations and remissions. The frequency and severity of attacks may reduce with time, but there is no possible way of predicting the evolution of these patients in terms of morbidity and possible mortality. Young onset and male patients have been shown to confer a worse prognosis while a severe deterioration is seen in 20% of patients. Some possible complications include bowel perforation, extensive thrombotic events, or rupture of arterial aneurysms and may lead to death. Fortunately mortality does not appear to be higher than in general population.
Morbidity, however, may be high and may lead to significant disabilities. Irreversible retinal vasculitis and blindness, sterile meningoencephalitis or severe arthritis may occur and are severe complications of Behçet´s syndrome.
Behçet´s syndrome is still one of the most frequently encountered causes of endogenous uveitis. The introduction of ciclosporin has greatly assisted in the management, and prognosis of visual manifestations. The encouraging results with the use of Interferon-alpha in the treatment of this syndrome may further improve the prognosis in certain cases, particularly when further research on dosage standardization has been completed.

The treatment of the mucocutaneous and eye manifestations has improved significantly in recent years. However, arterial or neurological manifestations may still present significant management problems.

Prevention

The unknown aetiology of Behçet´s Syndrome is a significant handicap in the development of a preventative regimen for the disease. In absence of such knowledge and of a curative therapy, treatment is directed at the relief of symptoms and the prevention of complications. A multi-system disorder such as this is best managed with input from a multidisciplinary to ensure optimal outcome. All the immunomodulating agents that are used to prevent the attacks of the disease and complications have short and long-term seccondary effects. Only a rigorous planning and dosage will minimize undesirable effects.

There is conflicting opinion on whether Behçet´s patients should or should not be anticoagulated. Whilst anticoagulation may reduce the risk of thrombosis or embolism, it increases the risk of serious haemorrhage and is contraindicated in case of previous or suspected aneurysm formation. As such each case should be considered on its own merits.

Table 1 Diagnostic criteria for Behçet disease

Recurrent oral ulceration	Minor aphthae, major aphthae or herpetiform ulceration observed by physician or patient
Plus 2 of:	
Recurrent genital ulceration	Aphthous ulceration or scarring observed by physician or patient
Occular lesions	Anterior uveitis, posterior uveitis, or cells in vitreous humour on slit lamp examination or retinal vasculitis observed by ophthalmologist
Skin lesions	Erythema nodosum, pseudofolliculitis or papulopustular lesions examined by physician Acneform nodules observed by physician in patients not on steroid treatment
Positive pathergy test	Checked by physician at 24-48 hours

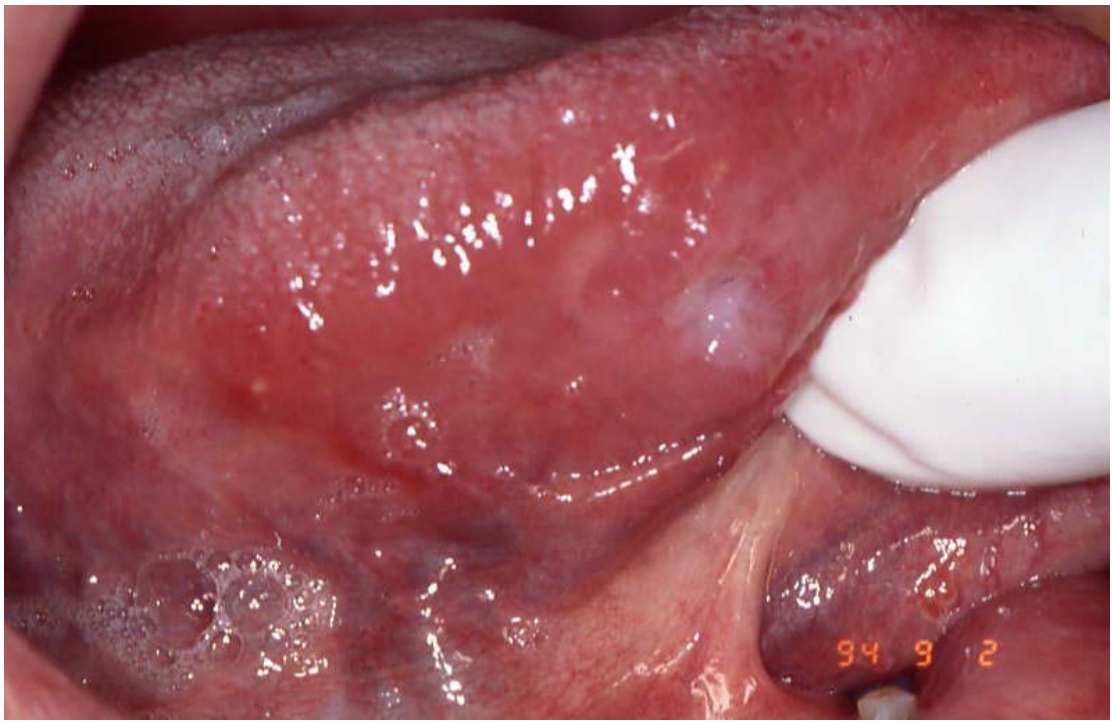

Figure 1. Oral lesion in a patient affected by Behçet's syndrome

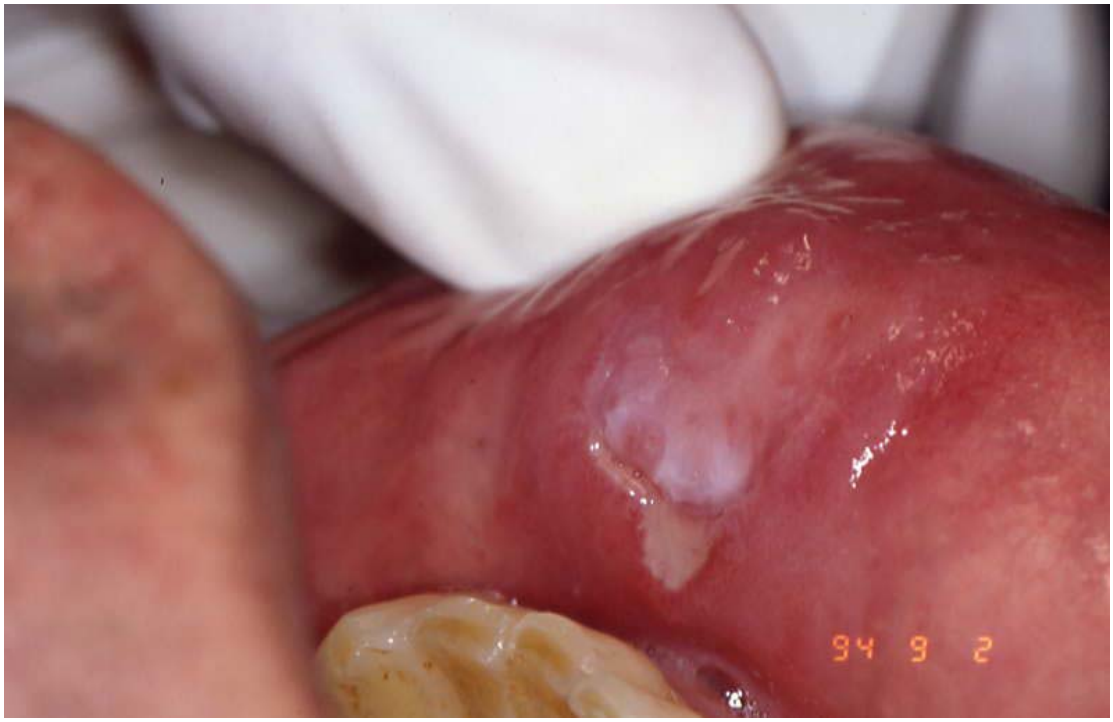

Figure 2. Labial lesion in a patient affected by Behçet's syndrome

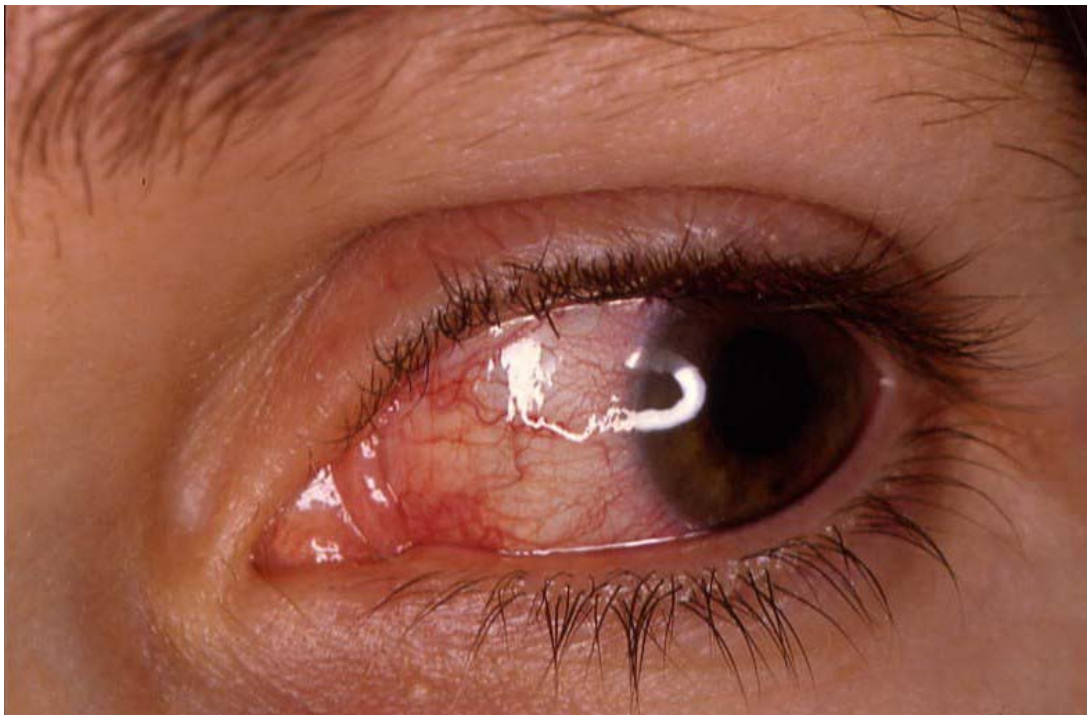

Figure 3. Eye lesions in a patient affected by Behçet's syndrome

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BURNING MOUTH SYNDROME

Definition

Burning mouth syndrome (BMS) is defined as a burning discomfort or pain affecting the oral soft tissues of psychogenic or unknown causation in people with *clinically normal, healthy oral mucosa in whom a medical or local dental cause has been excluded*.

A number of other terms have previously been used to describe what is now called BMS including -

- glossodynia
- glossopyrosis
- stomatodynia
- stomatopyrosis
- sore tongue
- oral dysaesthesia

The symptom of a burning mouth may represent a separate disease process where local or systemic factors are involved. In these cases the effective treatment of this disease process will result in its resolution. Thus local and systemic factors (i.e. infections, dermatological diseases with oral features such as lichen planus, allergies, ill fitting dentures, hypersensitivity reactions, hormone and vitamin deficiencies) and some drugs may cause the symptom of a burning mouth and should be excluded before formally diagnosing burning mouth syndrome. Confusingly, many research studies concerning people with symptoms of burning mouth do not distinguish those with burning mouth syndrome (i.e. idiopathic disease) from those with other conditions (such as vitamin B deficiency), making the results unreliable and difficult to interpret.

Epidemiology

Burning mouth syndrome predominantly seems to affect women, particularly after the menopause and its frequency seems to increase with age. Reported incidence and prevalence in general populations varies significantly according to diagnostic criteria employed: many studies have included people with the symptom of burning mouth rather than with BMS as defined above, and when this is taken into account, prevalence of 1% or less is more accurate.

Clinical presentation

Many patients will give a long history of burning mouth and may have already consulted a number of other health care professionals before seeking help from an oral physician. The burning sensation may be felt as either a continuous or intermittent discomfort which most frequently affects the tongue, and sometimes the lips or palate. Other oral mucosal sites may also be involved. Patients may describe the discomfort of BMS with words such as *tender*, *annoying* and *tiring*. Onset of the symptom may be sudden or gradual over months and it has been suggested that severe life events are associated with the onset of BMS

In patients with BMS, no oral mucosal lesions will be detected on examination.

Up to 50% of patients with BMS report an associated sensation of oral dryness which is not confirmed on investigation. Some of these may also notice increased thirst. In addition affected patients may report altered taste sensation - either with reduction in taste perception or the presence of a persistent unusual taste, most frequently bitter or metallic. Unlike most other oral disorders, BMS usually does not interfere with sleeping, and drinking or eating may temporarily reduce the severity of symptoms. Patients may have associated anxiety or depression. There is some research which suggests that patients with BMS are significantly more likely to score highly for various personality traits such as somatisation, obsessive-compulsive, personal sensitivity when compared with unaffected control subjects.

Aetiopathogenesis

The cause of BMS is unknown and to date there have been no good aetiological studies. It is a medically unexplained symptom.

Suggested possible causal factors for BMS include hormonal disturbances associated with the menopause, psychogenic factors (including anxiety, depression, stress, life events, personality disorders, and phobia of cancer) and nerve abnormalities. It has been suggested that in some subjects who have sustained damage to the facial nerve and have a heightened taste sensation (the so-called ‘supertasters’), the balance of taste sensation is upset and phantom tastes and a burning sensation can ensue owing to lack of the normal inhibitory function of the facial nerve.

Whilst many patients with BMS show clinical features of anxiety, depression, and somatisation or various personality traits it is often difficult to clarify whether they have occurred as a reaction to the distress associated with BMS or are actually involved in its development.

Diagnosis

The diagnosis is essentially one of exclusion.

An in-depth social history should always be obtained from patients with symptoms suggestive of BMS. This explores social factors which may be contributing to psychological stresses which may be involved in the patient's symptoms, as well as the coping strategies employed to deal with them.

The patient's health and medication will be thoroughly reviewed to exclude other causes of a burning mouth (Table 1). There are large number of medications which can cause a dry mouth and subsequent oral mucosal soreness.

Investigations are employed to confirm that the affected patient does not have one of the conditions which may give rise to symptoms similar to those of BMS (Table 1). They should only be undertaken if the detailed history and examination indicates that they are appropriate. Table 2 shows a number of investigations which might currently be considered in a patient with symptoms of a burning mouth.

Table 1- Suggested potential causes for the symptom of a burning mouth

LOCAL CAUSES

- Dry mouth (xerostomia)
- Mucosal disorders – geographic tongue (erythema migrans), lichen planus etc
- Trauma to oral mucosa from (e.g. poorly fitting dentures)
- Repetitive oral habits (such as “tongue thrusting”)
- Gastro-oesophageal reflux disease
- Sensory nerve damage (e.g. due to trauma)

SYSTEMIC MEDICAL CAUSES

- Vitamin B12, folate, iron deficiencies
- Medication (e.g. angiotensin converting enzyme [ACE] inhibitors such as captopril)
- Immunologically-mediated diseases (e.g. Sjogren’s syndrome)
- Psychogenic disorders (e.g. depression, anxiety, fear of cancer)
- Psychosocial stresses (e.g. stressful life events such as bereavement)
- Diabetes mellitus
- Menopause

Table 2 – Investigations and assessment which might currently be considered in patients with symptoms of a burning mouth.

- Full blood count - to exclude anaemia
- Iron, vitamin B12 and red cell folate levels – to exclude deficiency
- Random blood glucose levels – to exclude diabetes mellitus
- Measurement of salivary flow – to exclude a dry mouth
- Immunological blood investigations – to exclude Sjogren’s syndrome
- Oral biopsy - if an oral lesion is found on examination
- Assessment of denture fit and function
- Psychological assessment – to investigate possible depression or anxiety

Treatment

If any obvious causative factors contributing to the symptoms of a burning mouth are identified then these should be further investigated and corrected appropriately. In the absence of local or systemic causes then the diagnosis of BMS is likely and the patient needs to be thoroughly reassured that there is no other cause.

Patients with BMS often feel that they have insufficient information about the condition and verbal information should be reinforced with well-designed written information.

Management of this condition is hampered by a lack of good quality trials of treatment. There is an evidence-based review of interventions in BMS published in Clinical Evidence[1] which is regularly updated, in addition to a Cochrane review[2] which may be helpful for the interested reader.

Cognitive behaviour therapy (CBT) has been shown to have some benefit in this condition but is complex and clinically intensive. This involves the identification of maladaptive thought processing and it attempts to change this in a positive way.

Other treatment modalities which may be considered in BMS patients which have been used but so far do not have good quality evidence for efficacy include antidepressants, vitamins or dietary supplements such as alpha lipoic acid, analgesic sprays or mouthwashes such as benzydamine hydrochloride and, in post menopausal female patients, hormone replacement or topical oestrogen applied to the oral mucosa. Where a dry mouth is a prominent symptom then saliva substitutes may be considered.

Outcome

The natural history of BMS has not been clearly defined but there are suggestions that partial spontaneous remission may occur in one third to a half of affected patients within 6-7 years of symptom onset. Improvement in BMS may be expected in about one third of cases, particularly in those patients with intermittent symptoms.

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DENTURE RELATED STOMATITIS

Definition

Denture-related stomatitis indicates an inflammatory process of the mucosa that bears a complete or partial removable dental appliance, typically a denture.

Since it was described as “sore mouth under plates”, several terms have been used in the past to define this condition: “chronic denture palatitis”, “stomatitis prothetica”, “denture related candidiasis” “denture-induced stomatitis” and “denture stomatitis”. The classical expression “denture sore mouth” is being abandoned as most patients show asymptomatic lesions.

Nowadays, “denture stomatitis” stands for a mild chronic erythematous candidiasis, usually seen after middle age as erythema limited to the area beneath an upper denture, with the presence of the denture as the only common etiologic factor to these situations. It is not caused by allergy to the denture material.

Epidemiology

Denture stomatitis is a common condition: findings from several studies suggest that it can affect as many as 35-50% of persons who wear complete dentures. The prevalence of denture stomatitis among those wearing partial dentures is markedly lower than among complete denture wearers, whose rank goes from 10% to 70% depending on the population studied.

No racial or sex predilection exists, although some authors have described a higher prevalence among women.

This disorder is more frequent among elderly people, as they are more likely to wear removable dentures. However, there are reports that could not prove significant differences in the prevalence according to the age of the subject. Paradoxically, several authors have described a significant fall in the prevalence of denture stomatitis in older patients. The highest prevalence, though, has been reported in aged people, especially those living in nursing facilities.

Clinical presentation

Denture stomatitis lesions may show different clinical patterns, and are more frequently found in the upper jaw, especially on the palate. The absence of denture stomatitis in the lower jaw is probably due to the washing action of saliva.

Despite the fact that denture stomatitis is frequently asymptomatic, patients may complain of halitosis, slight bleeding and swelling in the involved area, or a burning sensation, xerostomia, or taste alterations (dysgeusia). These symptoms occur, with variable intensity, in 20% to 70% of patients with denture stomatitis. In these situations, the patient usually does not relate the use of a denture to the experienced symptoms.

Staging Different classifications have been proposed, but the reference classification for denture stomatitis is the one suggested by Newton in 1962, based exclusively on clinical criteria:

Newton´s type I: pin-point hyperaemic lesions (localized simple inflammation) (Fig.1)

Newton´s type II: diffuse erythema confined to the mucosa contacting the denture (generalized simple inflammation) (Fig.2)

Newton´s type III: granular surface (inflamatory papillary hyperplasia) (Fig.3).

Related disorders:

Denture stomatitis can occasionally be associated with different lesions of fungal origin such as angular cheilitis, median rhomboid glossitis and candidal leukoplakia.

Aetiopathogenesis

The aetiology is best considered multifactorial, but denture wearing, especially when worn during the night, represents the major causative factor.

Among the aetiological factors that should be considered are:

1. Prosthetic factors

- No denture stomatitis can exist without a prosthesis. Ill-fitting, traumatic, badly-maintained dentures have been considered as the most frequent causes of denture stomatitis.
- Prosthetic traumatism is favoured by denture functional deficiencies, like:
    - Occlusal alterations
    - Vertical dimension alterations
    - Retention alterations
    - Unstable prosthesis

The type of material employed for its construction (Newton´s type III is 5-fold more frequent with acrylic dentures than with metallic ones) also condition the development of denture stomatitis.

2. Infectious factors Denture can produce a number of ecological changes that facilitate the accumulation of bacteria and yeasts.

- Bacteria proliferate. Certain bacterial species, like *Staphylococcus species*, *Streptococcus species*, *Neisseria species*, *Fusobacterium species*. or *Bacteroides species* has been identified in patients with denture stomatitis, although no direct relationship between bacteria and the aetiology of denture stomatitis could be proved.
- *Candida species,* particularly *Candida albicans,* have been identified in most patients. Patients with denture stomatitis show higher intraoral concentrations of fungi than individuals without this disorder and the lesions objectively improve after antifungal drug administration. However, the role of this organism as the sole aetiologic factor remains unclear.

Predisposing factors for oral candidosis include:

1. Systemic factors
    a. Physiological. (advanced age)
    b. Endocrine dysfunctions.
    c. Nutritional deficiencies.
    d. Neoplasias.
    e. Immunosuppression.
    f. Ample spectrum antibiotics.

2. Local factors
    a. Antimicrobials and topical or inhaled corticosteroids
    b. Carbohydrate rich diet
    c. Tobacco and alcohol consumption
    d. Hyposalivation
    e. Deficient oral hygiene
    f. Wearing dentures (especially through the night)

Diagnosis

The clinical presentation of erythema and oedema on the palatal mucosa covered by the denture base (but not beyond) is a diagnostic finding. A smear of the palate stained with

KOH or periodic acid-Schiff can demonstrate the presence of *Candida species*. Other techniques for identifying fungal isolates such as imprint cultures may also be applied.

Treatment

- Good oral hygiene is mandatory. The mouth must be kept as clean as possible and a thorough rinse after meals should be performed.
- Local factors which promote growth of yeasts, such as smoking or wearing the dentures throughout the night, must be discouraged.
- Dentures should be removed for as long as possible and definitely overnight. Dentures should be brushed in warm, soapy water and soaked overnight in an antiseptic solution such as bleach (10 drops of household bleach in a denture cup), chlorhexidine (not when the denture has metal components), or in any solution suitable for sterilizing baby´s feeding bottles. Benzoic acid containing products should be avoided as they induce changes in the composition of acrylic materials.
- Denture fitting and occlusal balance should be checked to avoid trauma. A new prosthesis should be made, if necessary. Tissue conditioning agents are porous materials easier to colonize than acrylic, so they are not recommended for these patients. If there is no other choice, an antifungal agent, like nystatin, miconazole or ketoconazole may be incorporated to the agent. Dentures must be adequately polished and glazed, as pores increase denture contamination by oral microorganisms
- Newton`s type I and II denture stomatitis have been successfully treated with low energy lasers to reduce inflammation of the supporting mucosa. Inflammatory papillary hyperplasia usually needs to be surgically removed (by scalpel, cryosurgery, electrosurgery or with a laser beam) before the denture is placed, although mild cases may respond to antifungal treatment.
- Antifungal medications are recommended when yeasts have been isolated, or when lesions do not resolve with hygiene instructions.

First choice treatment is the topical application of nystatin or miconazole. Resistance to nystatin is rare; the drug is administered as an oral suspension**,** with an unpleasant taste and can induce gastrointestinal problems and hypersensitivity. Miconazole is available as gel, varnish, lacquer and chewing gum. It also provokes gastrointestinal alterations and hypersensitivity, but it tastes better. Miconazole enhances warfarin effect.

Systemic antifungal drugs (i.e. fluconazole, itraconazole, ketoconazole), are almost exclusively reserved for patients with systemic factors that condition the development and persistence of candidosis, such as immunosuppression or diabetes.

Prognosis and complication

If untreated, denture stomatitis can cause soreness and palatal inflammatory papillary hyperplasia and may lead to poorly fitting dentures in the future.

The administration of topical antifungal therapy, removal of mechanical traumatism caused by the denture and reinforcement or hygienic measures, ease the disappearance of the lesions. However, local recurrences are frequent if aetiopathologic factors persist.

The prognosis of this disorder is good, as malignant transformation has not been reported, although continuous aspiration and swallowing of *Candida species* may rarely have potentially fatal consequences in immunocompromised patients.

Prevention

It is mandatory to include denture stomatitis prevention in oral health care programmes. Dental professionals working with geriatric patients must promote this preventive programmes among all health care workers, home caregivers, members of the patient's family and, of course, the patients themselves.

A preventive programme should include:

- A routine basis inspection of the oral cavity for screening for this disorder, even when the lesions are asymptomatic.
- Properly denture sanitization and perform good oral hygiene
- Appropriate denture-wearing habits, instructing the patient to take his/her denture out of the mouth for 6-8 hours each day
- Patients with partial dentures should undergo periodic professional plaque control

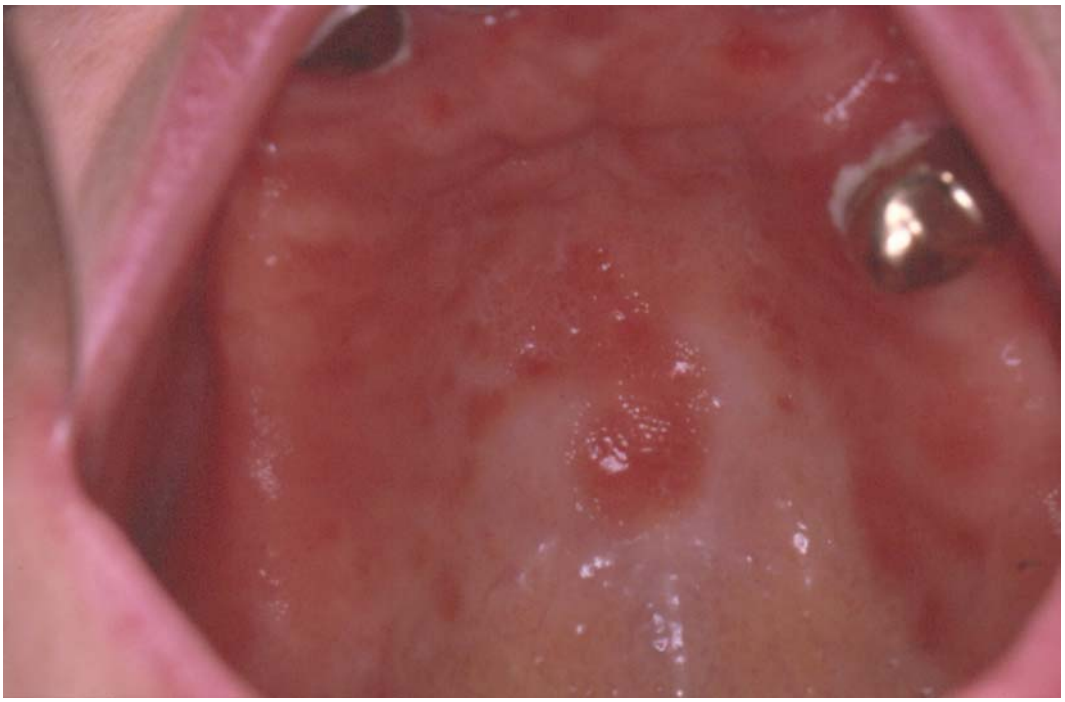
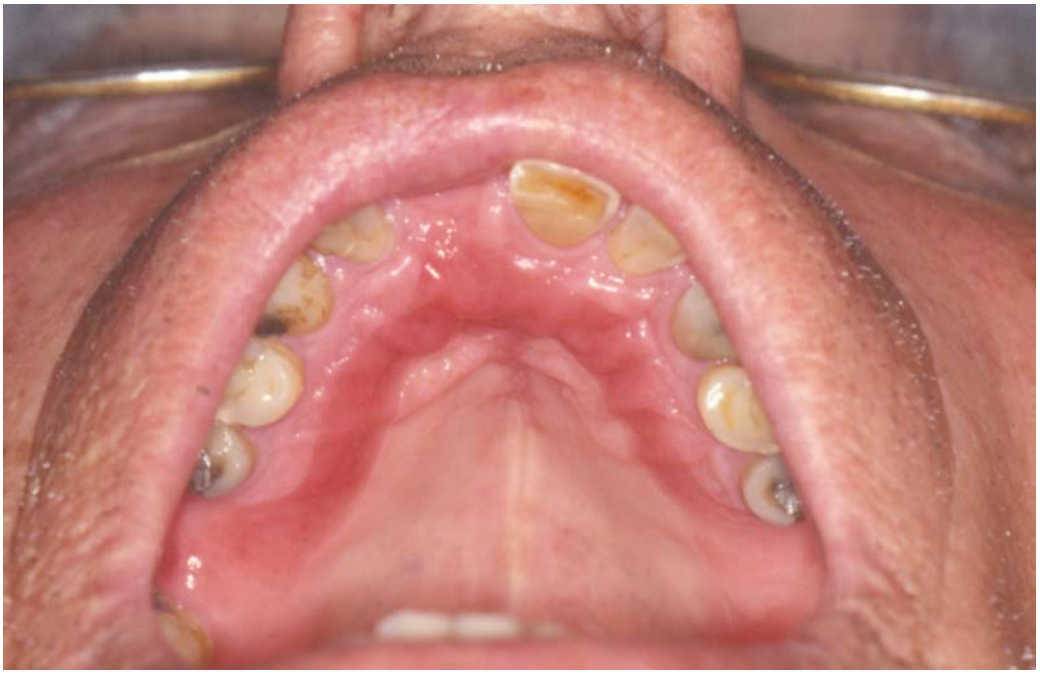


Figure 1. Newton´s type I stage showing hyperaemic foci



Figuren 2. Newton´s type II stage showing diffuse erythema confined to the mucosa contacting the denture.

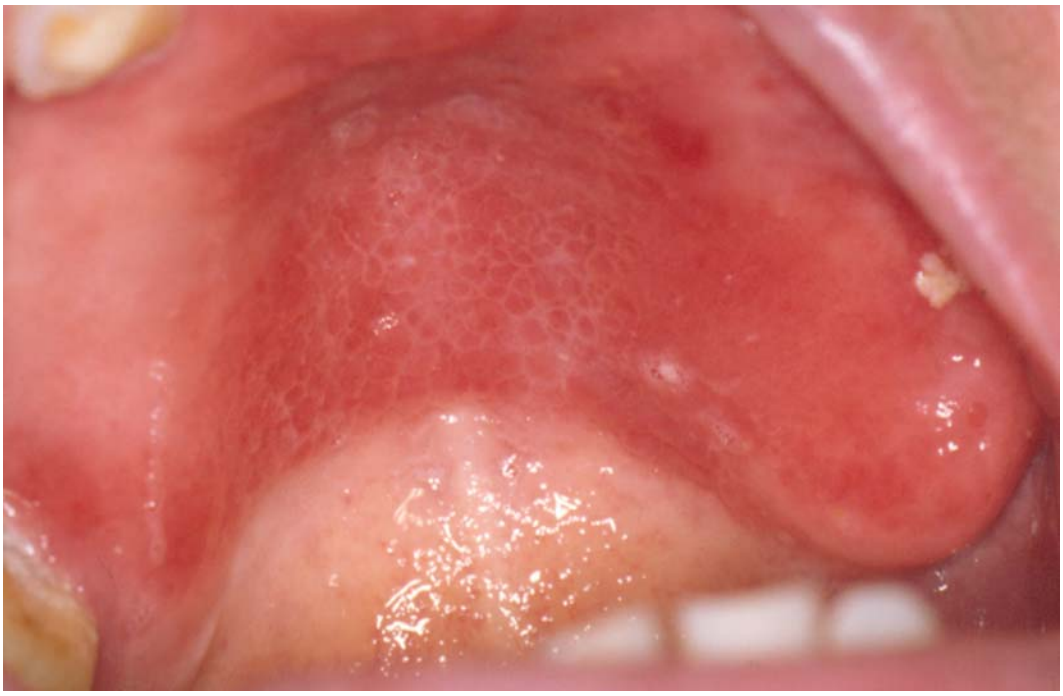


Figure 3. Granular type of stomatitis (Newton´s type III).

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DRUG-INDUCED GINGIVAL OVERGROWTH

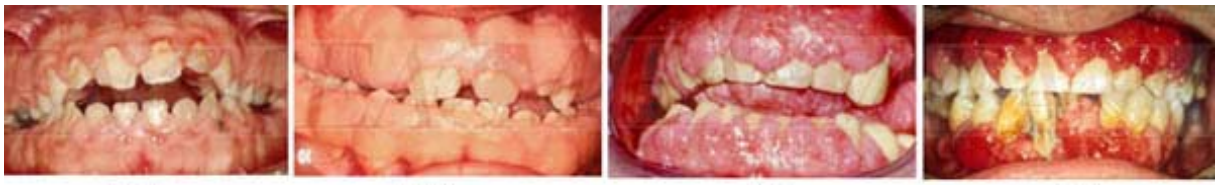
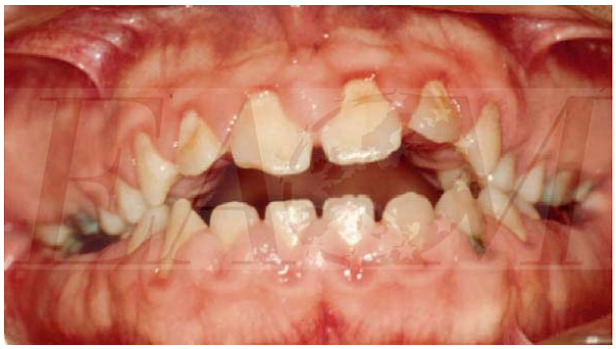
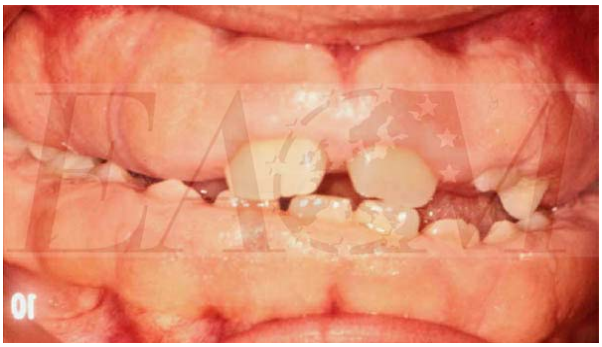


Fig.1 Fig.2 Fig.3 Fig.4

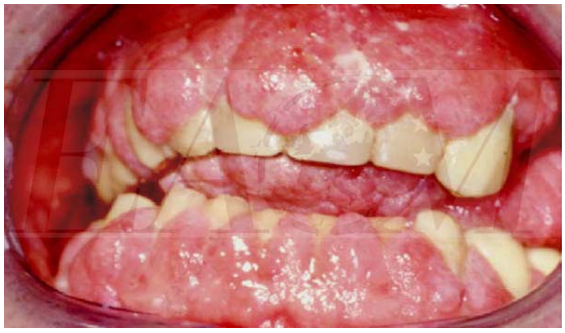
Definition

Many terms have been used to describe gingival overgrowth. The expression *gingival hyperplasia* ("abnormal increase in the number of normal cells in a normal arrangement in an organ or tissue, which increase in volume") and *gingival hypertrophy* ("enlargement or overgrowth of an organ or part due to an increase in size of its constituent cells") have been also used, although gingival overgrowth is the general term that better describes this iatrogenic condition.
Drug-induced gingival overgrowth occurs as a side effect of some systemic medications. The pharmacological agents mainly associated with gingival overgrowth are:

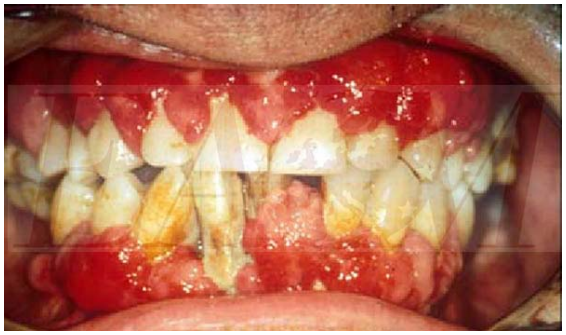




• phenytoin (Fig.1 and Fig.2), a drug used for the management of epilepsy, and other anticonvulsants such as sodium valproate, phenobarbital, vigabatrin;



• ciclosporin (Fig.3), an immunosuppressant drug used to reduce organ transplant rejection;



• calcium-channel blockers (Fig.4) (nifedipine, verapamil, diltiazem, oxodipine, amlodipine), a group of anti-hypertensive drugs.

Other drugs, such as antibiotics (erythromycin) and hormones, have been also associated with this side effect.

Epidemiology

Not all the patients using these agents are affected by gingival overgrowth, and the extent and severity are variable in such patients.

Phenytoin-induced overgrowth may be present in 50 to 100% of patients treated with such drug, whereas ciclosporin and calcium channel blocker-induced overgrowths seem to be less common, ranging from 15-85% and 10-30% respectively.

Although gender and age may not be relevant risk factors for phenytoin-induced overgrowth, among patients taking ciclosporin and/or nifedipine, males may be at higher risk than female.

The relationship between age and gingival overgrowth is uncertain; some authors have described young age as risk factor, but other studies have not confirmed such finding. Age is not an applicable risk factor for the calcium channel blockers since the use of the drugs is usually confined to the middle aged and older adult. Nevertheless, in patients treated with both ciclosporin and calcium channel blockers, age has been identified as a risk factor.

A correlation with dosage, duration, drug concentrations (in blood and whole saliva) and severity/extent of gingival enlargement has also been suggested, but so many variables (sampling technique, pharmacokinetic factors) can influence this aspect, that it remains controversial. However, it has been recently reported that patients treated with ciclosporin solution experience earlier onset of gingival changes and more extensive overgrowth than patients using capsules.

Clinical presentation

The gingival overgrowth usually starts from the papillary regions. As the process develops, the papillae increases in size and the margins and gingival attachment may also became involved. The anterior segments and the labial gingiva are most commonly involved, but the enlargement may also be observed in the molar regions, particularly in the late stages of disease. Some case reports have also described overgrowth of edentulous ridges and elsewhere.

Clinical features of the gingival overgrowths are very similar, independent of the drug implicated. However small differences have been described: in cases due to anti-epileptic drugs, gingivae are firm and pale because of the conspicuous fibrous component, while other drug-induced gingival enlargements are characterised by a nodular lobulated spongy aspect and secondary inflammation that may induce oedema, ulcerations and bleeding on brushing.

Etiopathogenesis

The pathogenesis of drug-induced gingival overgrowths is still not completely understood. It has been demonstrated that gingival enlargement has a multifactorial nature and is affected by factors such as age, demographic variables, genetic predisposition, oral hygiene status, pharmacokinetic variables and molecular and cellular changes in gingival tissues. Ciclosporin, phenytoin and calcium-channels blockers can influence the metabolism of some age-dependent hormones (i.e. testosterone) which could have a direct effect on gingival cells populations.

Some studies have demonstrated that patients developing gingival lesions have high frequency of particular HLA antigens and genetic markers (cytochrome P450, HLA-DR2,) and this appears to be related to a genetic predisposition for this pathology. Furthermore, it has also been reported that patients who expressed genetic markers such as HLA-B37or HLA-DR1, are afforded some degree of protection against gingival overgrowth.

Changes in gingival contour seen in drug-induced gingival overgrowth may also be exacerbated by plaque-induced gingival inflammation, through a mechanism of mechanical and chemical chronic irritation.

Even drug variables such as dose, duration of therapy, serum and salivary concentration appear to be related to the pathogenesis of gingival enlargement.

Concomitant use of drugs implicated in gingival overgrowth is likely to increase the incidence and degree of gingival lesions, although controversy still exists. A direct effect of ciclosporin, phenytoin and nifedipine (or metabolites) on the activity of some gingival cells (i.e. fibroblasts) has been demonstrated. Enhance of cells growth and of production of proteins as collagens has been observed in cultures of human gingival cells directly stimulated with these drugs.

Diagnosis

The diagnosis of drug-induced gingival overgrowth is mainly based on the clinical appearance of the gingivae and on the medical history.

The histopathological features of the phenytoin drug-induced gingival enlargements are mainly characterised by proliferation of morphologically normal fibroblasts and by an increased amount of collagen.

The histopathological features of the other drug-induced gingival enlargements are similar and characterised by a collagenous connective tissue with little or no inflammatory exudates. The connective tissue is highly vascularised and there are focal accumulations of inflammatory infiltrates dominated by plasma cells, that may be suggestive of a neoplastic process.

Treatment

Treatment of drug-induced gingival overgrowth includes surgical and/or non-surgical therapies.

Non-surgical treatment, where it is possible, is based on the interruption, modification of the dosage or replacement of the drugs.

In patients treated with ciclosporin, it seems that the contemporary use of the antibiotic azithromycin may decrease the severity of gingival overgrowth. Furthermore, in adult organ transplant patients, dosages of both prednisolone and azathioprine appeared to afford the patients some degree of “protection” against gingival overgrowth and may also reduce the severity of this side effect.

Good oral hygiene associated with the use of chlorhexidine oral rinses and frequent plaque and calculus removal procedures, could help to reduce the degree of gingival overgrowth. After the interruption of therapy or the replacement of drugs, follow -up of 6-12 months is important to evaluate the resolution of gingival overgrowth and/or the necessity of a surgical treatment.
Surgical treatment consists of removing gingival hyperplastic tissues with periodontal surgical techniques of gingivectomy and/or periodontal flaps. Gingivectomy is the treatment preferred when the gingival overgrowth involves small areas (up to six teeth), there is no evidence of attachment loss and there is at least 3 mm of keratinized tissue. The periodontal flap is preferred when the gingival overgrowth involves larger areas (more than six teeth) and there is evidence of attachment loss combined with osseous defects. CO2 or argon-laser surgery has been proposed as surgical treatment of gingival overgrowth because of decreased surgical time and rapid post-operative haemostasis.
Good oral hygiene for preventing or retarding the recurrence of the gingival overgrowth is important after surgery.

Prognosis and complications

Recurrences are frequent, particularly in patients with less than optimal plaque control and when the drug regimens cannot be modified or reduced.

As reported above, the presence of dental plaque, orthodontic and prosthetic appliances, or imperfect restorations may contribute to increase the inflammatory changes of the gingivae.
The enlarged gingivae are not only aesthetically displeasing but can occasionally interfere with occlusion, mastication and speech.

Prevention

Good oral hygiene may help to prevent the onset and development of gingival enlargement.

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DRY MOUTH

Definition

Dry mouth and oral dryness are general terms that encompass 2 medical entities: xerostomia and hyposalivation.

Xerostomia is the *subjective* complaint of oral dryness, and is medically classified as a symptom.

Hyposalivation is the *objective* reduction in salivary secretion, as the consequence of reduced salivary gland function.

Generally, these conditions are closely related to each other: a reduced salivary flow is the most frequent cause of xerostomia, and it is generally accepted that hyposalivation causes the symptom of oral dryness when salivary secretion rate is reduced by at least 50%. Nevertheless, in certain cases these entities do not seem to be interrelated, since some patients complaining of dry mouth do not show any objective evidence of a reduced salivary flow and, in turn, some patients with proven salivary gland hypofunction do not report symptoms of xerostomia.

It should be stressed that the variability of normal salivary secretion rate in the population is very large. Ideally, reduction in salivary secretion should be established on an individual basis when compared to the normal secretion of every single patient in the past (Figure 1).

Epidemiology

Population studies on xerostomia are based on questionnaires asking if and how frequently the screened persons suffer from dry mouth symptoms. According to recent reports the prevalence (occurrence) of xerostomia (which means persons complaining of dry mouth either “frequently” or “always”), in the adult population is as follows:

- 24% of females and 18% of males, 19-88 years old Rochester (New York, USA) residents.
- 27.3% of females and 21.3% of males, 20-80 years old Swedish residents.
- 29% of 18-83 year old New York City residents.
- 9.7% of adult Barcelona (Spain) residents.

Xerostomia is especially frequent in the elderly. In this specific population, xerostomia has been reported to occur in 17 to 39% of the persons aged 65 years or more. In addition, xerostomia is more frequent among women than men.

Based on available data, a conservative analysis of the occurrence of xerostomia in the developed world shows a prevalence of 80 million people. The following table summarises the results of the analysis:

Age (years)	% of total population	Population (millions)	% of xerostomia complainers	Number of xerostomia complainers (millions)
20-40	25	285	5	14
40-60	20	230	10	23
60 and more	25	285	15	43
Total	**70**	**800**	**10**	**80**

As to the prevalence of hyposalivation, very few population-based data are available. This condition has been found in over 22% of older South Australians and in almost 12% of Israeli elderly people.

Clinical presentation

Saliva is a crucial protective factor of the oral cavity and enables its normal functioning (speech, alimentation) due to its lubricatory and defensive properties.

- Taste perception is facilitated by saliva carrying food particles onto the taste buds in an appropriate dilution.
- Salivary amylase and lipase start the digestion of starch and fat.
- Saliva is also important in the formation of the food bolus, assisting in food mobility and reducing friction between the different oral structures (teeth, tongue, cheeks, lips) and between these structures and foreign elements (food, dental prostheses).
- Salivary lubrication, repair, lavage, antimicrobial and buffering properties contribute significantly to the maintenance of oral hard and soft tissue integrity.

The full accomplishment of these functions depends on proper salivary flow rate and composition.

Consequently, hyposalivation may induce a variety of oral hard and soft tissue pathological changes, generally classified as “complications”.

The lower the salivary flow rate, the less salivary defense and lubrication components enter the oral cavity.

Soft tissues changes:

- The mucosal tissues may become painful, “burning”, dry and atrophic. A typical complication of hyposalivation is the occurrence of cracked lips.

- Hyposalivation may trigger a painful salivary gland infection called “sialoadenitis”, characterized by facial swelling, pain and, in certain cases, fever. The most frequent salivary gland infection is located on the parotid glands and is therefore named “parotitis”.
- Another frequent oral infection in patients affected by hyposalivation is candidosis. It is a fungal infection due to the *Candida* species of fungi, which can clinically present as white patches, redness (erythema and/or atrophy) and burning of the oral mucosa. Candidosis is more common in denture wearers.

Hard tissues changes:

An increased rate of dental caries with a distinctive cervical pattern of decay, which is extremely difficult to treat, is typically seen.

Other symptoms:

- Denture wearers often complain of severe discomfort with their dental appliance.
- Decreased salivary secretion often leads to difficulties in chewing, swallowing and speaking and a diminished taste sensation. Furthermore, patients frequently have to wake up at night repeatedly to sip water.
- Another relevant symptom that have been related to hyposalivation is halitosis (bad breath; oral malodour)

In summary, the consequences of a reduced salivary flow compromise not only the biological integrity of the individual and the oral health status but also the general quality of life and well-being and can lead to reclusion and loneliness.

Etiopathogenesis

Xerostomia, as the symptom of oral dryness, results most frequently from hyposalivation.
Other causes of xerostomia not related to hyposalivation are habits (such as mouth breathing), sensory impairment, and psychological or unknown (idiopathic) factors.
Hyposalivation can be caused by systemic diseases or by their treatment.

Systemic diseases as causes of hyposalivation

Sjögren’s syndrome (SS), an autoimmune disease causing oral and ocular dryness, is the second most frequent cause of hyposalivation.
Hepatitis C virus (HCV) infection is estimated to affect about 3% of the world population. HCV-infected patients may present a chronic inflammation of the salivary glands, which may lead to hyposalivation. This condition assumes particular importance in those nations where HCV infection is common.
Others diseases with associated hyposalivation are Alzheimer's disease, autonomic neuropathies, cystic fibrosis, depression, diabetes, graft-versus-host disease, HIV infection, sarcoidosis and others.

Medical treatments as causes of hyposalivation

Drug induced hyposalivation is the most frequent type of hyposalivation. At least 400 kinds of medications have been reported to cause dry mouth. Salivary flow is particularly reduced when two or more hyposalivatory drugs are taken simultaneously. As appreciated in the following listing, many of these agents are taken for long periods of times, often lifelong, and their deleterious effects increase with time.

List of xerogenic medications
•Cardiovascular agents, including antihypertensives drugs
•Tranquilizers and hypnotics
•Antidepressants
•Anti-psychotic agents
•Amphetamine derivatives
•Anticonvulsants
•Anti-Parkinsonian drugs
•Some gastro-intestinal and genitourinary systems agents
•Respiratory system and anti-allergic agents, including antihistamines
•Some steroidal and nonsteroidal anti-inflammatory drugs, anti-infective agents and narcotic analgesics
•Anti-neoplastic agents

Head and neck radiotherapy to treat head and neck cancer, accounts for the third most frequent cause and results often in the most severe type of hyposalivation.
Other therapies inducing hyposalivation are antineoplastic chemotherapy and bone marrow transplantation.
The question of whether age, *per se*, is a causative factor of hyposalivation has not been completely determined. However, it is clear that increased age is mostly accompanied by coexistent diseases and medication intake, many of them produce xerostomia.

Diagnosis

Xerostomia

The diagnosis of xerostomia is based mainly on a thorough questionnaire. In the absence of spontaneously expressed complaints, astute clinicians may suspect the occurrence of xerostomia, based on relevant anamnestic (historical) and clinical findings, such as medication intake, complaint of bad breath, extensive and/or recurrent dental caries, or the presence of oral fungal infections (candidosis).
Relevant questions to ask are:

- Have you had a daily feeling of dry mouth for more than 3 months?
- Have you had recurrently or persistently swollen salivary glands?
- Do you drink liquids to aid in swallowing dry food?
- Is the amount of saliva in your mouth too much, normal or too little?
- Do you wake up at night to drink liquids?

Hyposalivation

Hyposalivation may be diagnosed with the aid of salivary collection tests (called sialometry), while other tests as scintigraphy or sialography can be useful to further assess salivary glands. Salivary flow rate should be measured by standardized techniques. As salivary secretion fluctuates between minimal and maximal rates during the day, it is important to assess the salivary secretion consistently at an established time of the day, in order to properly examine the evolution of the condition and its treatment in every patient.

Whole saliva can be collected by spitting, blotting, suctioning or draining the oral fluid. In this case, the collected fluid represents the saliva secreted jointly by all salivary glands and other materials present in the mouth. It is also possible to collect separately saliva secreted by each of the major salivary glands - parotid, submandibular, and sublingual – or by the minor salivary glands, which are spread throughout the oral mucosa.

Salivary secretion can be assessed in unstimulated or stimulated conditions. The stimuli that enhance salivation are related to eating: tasting, smelling or seeing food, and chewing. Therefore it is crucial to consistently assess salivary function at fixed periods after such stimuli. Most units assess whole unstimulated sialometry.

Treatment

Xerostomia/hyposalivation are often chronic disorders, requiring long-term, if not a life-long, management by health care providers with experience in the field of Oral Medicine. Treatments of oral dryness are firstly aimed at restoration of normal salivary flow, due to the difficulty in obtaining an artificial fluid that mimics natural salivary properties, such as lubrication and oral soft and hard tissue defense. In addition, the hyposalivation-induced complications need to be managed (see under “Prevention”).

Pharmacological therapies

The parasympathetic agents pilocarpine and cevimeline are utilized primarily for the treatment of xerostomia in patients with Sjögren’s syndrome and after head and neck radiation. Even if very effective, pilocarpine administration is burdened by potential side effects involving gastrointestinal, cardiovascular, respiratory and urinary systems. Adverse effects must be strongly considered before administering pilocarpine.

Published data of trials on the effectiveness and safety of cevimeline in the treatment of xerostomia are few. However, it is expected that the drug adverse effects are similar to pilocarpine. Several other drugs have been tested to treat xerostomia. However, no conclusive evidence on the utility of these agents has been reported.

Non-pharmacological therapies

• Local treatment: These methods (mouthwashes, sugarless chewing gums and candies) are readily available and most oral dryness sufferers can use them. However, their effectiveness is

only temporary and often not satisfactory, thus demanding a permanent repeated use. As a consequence, patients' compliance is usually very low.

• Acupuncture: Recent studies have suggested that acupuncture may improve xerostomia with an increase in the salivary flow rate and sustained symptom relief.

• Electrostimulation;

A stimulator for inducing salivation by intra-oral neural stimulation has been tested and approved in the US. Theoretically, this therapeutic modality may represent the ideal treatment of hyposalivation since it might restore the salivary flow without dangerous side effects. However, the device is cumbersome and difficult to carry and stimulation is not constant (e.g. salivary secretion is not constantly enhanced): thus it is rarely used among xerostomic patients.

To overcome these problems, the European Commission is currently funding a European multi-national project, aimed at developing a long-lasting salivary stimulating miniaturized device, which will reside in the oral cavity and stimulate salivary secretion in a controlled and automatic fashion

Prognosis

When xerostomia is not caused by hyposalivation, the prognosis is related to the treatment outcome of the underlying factors, which are mostly psychological or sensory impairments. If these factors are severe and/or difficult to detect, their prognosis is poor and, as a result, also the prognosis of xerostomia is not encouraging.

The prognosis of xerostomia with a pure biological background (namely, hyposalivation-induced dry mouth) is related to the odds to treat successfully the factor involved. Grossly, the factor can be destruction of the salivary gland tissues (as in Sjögren's syndrome and head and neck radiation) or malfunction of the nervous control of salivary glands (as in drug-induced hyposalivation). The greater the degree of tissue destruction or of nervous malfunction, the lower are the odds of successful treatment outcome.

Tissue destruction is generally considered an irreversible condition, since the regeneration capability of salivary tissue is almost null. However, in most cases there is still remaining salivary functional tissue, which can be stimulated by drugs or other therapies to increase saliva secretion.

It may be possible to revert the neuro-functional effects of medications, by changing or stopping their administration. In some cases, salivary glands can be stimulated to compensate for the functional loss caused by xerogenic medications.

Prevention

The majority of the cases of xerostomia/hyposalivation are not preventable, as the causing factor is often unavoidable (e.g. drug induced hyposalivation) or cannot be eradicated (e.g. Sjögren's

Syndrome). However, few interventions may partially prevent hyposalivation induced by radiotherapy:

- A better arrangement of irradiation portals in order to spare contralateral major salivary glands, as well as the application of a novel dosimetric method (e.g. Intensity-modulated radiation therapy) may significantly reduce radiotherapy-induced salivary glands damage.
- Pilocarpine-treated patients undergoing radiotherapy to the head and neck have a lower frequency of oral dryness during and after treatment. A radiation protector, amifostine, has been reported to reduce the incidence of acute and delayed xerostomia. It can be administered by intra-venous infusion or sub-cutaneous infiltration. However, amifostine can present serious adverse reactions and its potential influence on tumor cells growth is still a matter of debate.

Furthermore, the management/prevention of hyposalivation's complications is another important issue, since in most patients salivary secretion cannot be fully restored, and they often experience the consequences of saliva absence or reduction.

Preventive approaches for hyposalivation-related dental caries include improved personal and professional oral hygiene, fluoride administration and dietetic adjustments. Dry mouth patients should visit the dental office at least every 3 months for oral examination, cleaning and fluoride application.

The frequency and intensity of fluoride application depends on the degree of hyposalivation. Patients with severe hyposalivation should rinse their mouth daily with a fluoride mouthwash, apply a fluoride gel on their teeth for 4 minutes once a week with the aid of a specially prepared dental appliance, and be given fluoride and/or chlorhexidine varnish as a professional application on their teeth. In addition, they should rinse their mouth with the antimicrobial agent chlorhexidine for one week (during one minute every day) out of every month. More intense and frequent rinsing with chlorhexidine may lead to microbial resistance to this agent and tooth staining.

The diet of people suffering of hyposalivation should be adjusted in such a way to reduce the risk of dental caries. The principles of such a diet include avoidance of snacks between meals and minimising the intake of sticky and sweet food and beverages.

Oral candidosis and bacterial sialoadenitis are generally easily managed with antimycotic and antibiotic drugs. Adequate fluid hydration and topical application of antimicrobial agents together with early diagnosis and therapy can prevent more serious progression of these conditions.

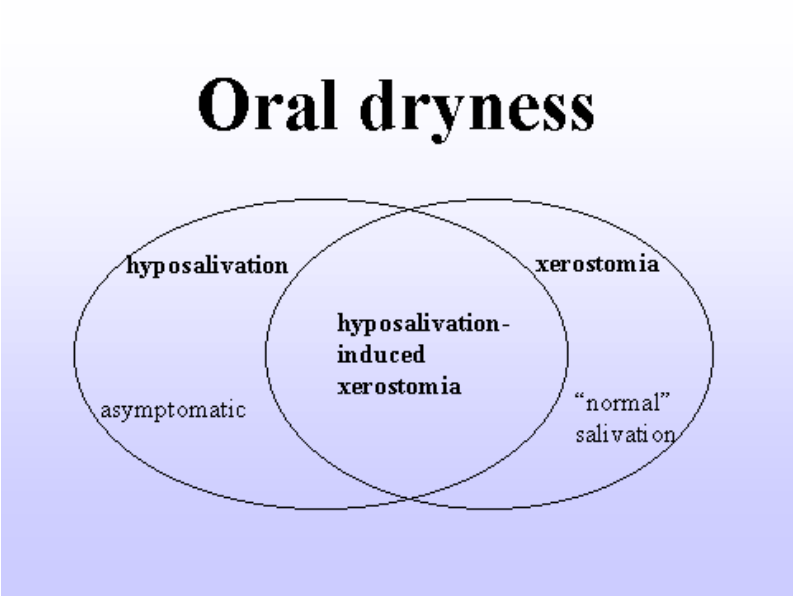

Figure 1. Scheme describing the typical distribution of patients suffering from dry mouth. They may be classified in 3 different groups:

a. Those having asymptomatic hyposalivation, i.e. a reduction in salivary secretion not significant enough to cause xerostomia.
b. Those with symptomatically significant hyposalivation, thus suffering of xerostomia.
c. Those suffering of xerostomia, but with no evident decrease in salivary secretion.

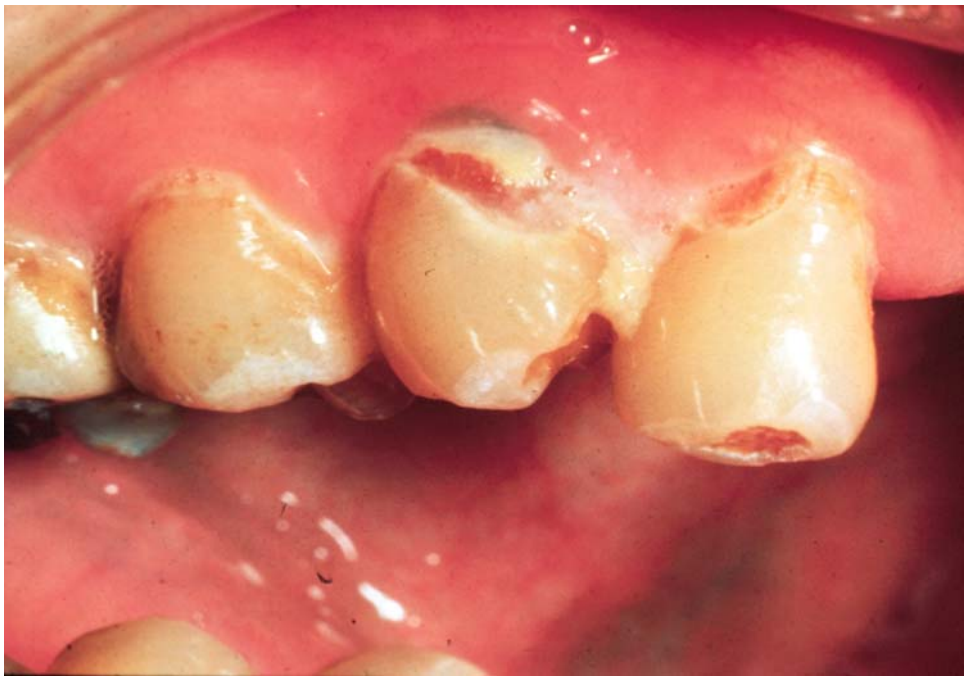

Figure 2. Cervical and incisal caries and plaque accumulation as a result of hyposalivation

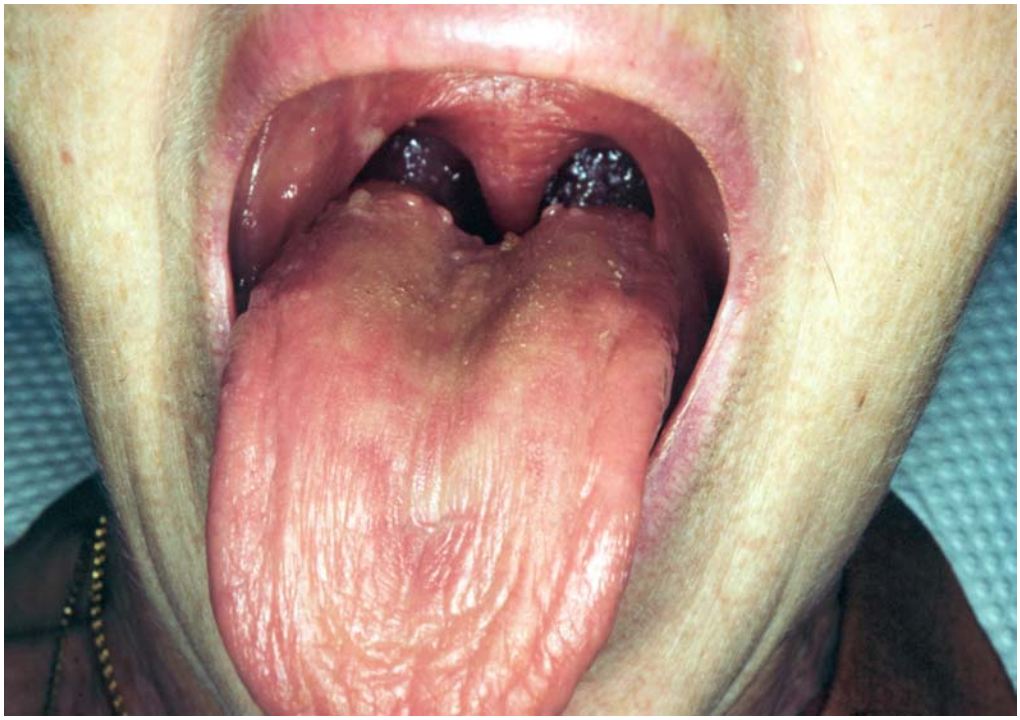

Figure 3: Tongue dryness resulting from medication intake

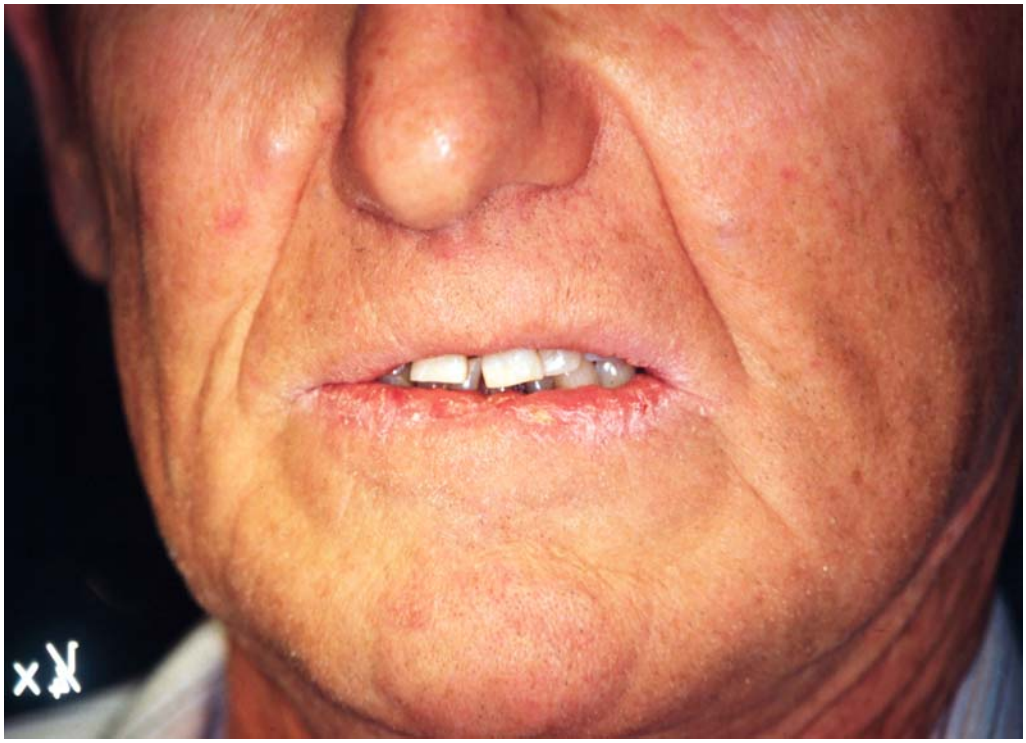

Figure 4. Cracked lips after radiotherapy to the head and neck

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Links

http://www.eastman.ucl.ac.uk/~eaom/clinical_support.html

http://www.nidr.nih.gov/health/newsandhealth/xerostomia.asp

http://www.nlm.nih.gov/medlineplus/mouthdisorders.html

DYSGEUSIA (BAD TASTE)

Introduction

The sensation of a bad, or unpleasant, taste is common – indeed most individuals have such symptoms, albeit only short-term. Long-standing unpleasant taste is infrequent and usually reflects local disease such as gingivitis and/or periodontitis.

Definition

Dysgeusia has been variously defined as a disgusting oral taste or altered taste sensation. *Hypogeusia* is defined as a reduction in all 4 taste modalities i.e. sweet, salty, sour and bitter. *Ageusia* occurs when none of these 4 taste modalities can be perceived. A spontaneous, continuously altered, often metallic taste in the mouth is usually drug related and has been termed “phantogeusia”. Severe long-standing dysgeusia can be clinically significant as it may lead to individuals losing interest in food and their altered dietary intake can result in nutritional deficiencies with exacerbation of any pre-existing disease.

Aetiology

A wide range of disorders can give rise to an unpleasant taste in the mouth. Most commonly a bad taste arises from gingival inflammation (e.g. gingivitis and acute necrotising ulcerative gingivitis), periodontal inflammation (e.g. periodontitis with or without lateral periodontal abscess), or infection about an erupting wisdom tooth (pericoronitis). Upper respiratory tract infections such as tonsillitis and sinusitis may also give rise to dysgeusia (often with accompanying oral malodour). Long-standing oral dryness (xerostomia) can cause a loss of taste and occasional dysgeusia.

There are a wide variety of other causes of dysgeusia (summarised in Table 1), however, these are rare and affected patients are likely to have significant, clinically-detectable disease.

Long-standing dysgeusia without a likely local or systemic cause (idiopathic dysgeusia) can be referred by individuals with an underlying mental illness such as depression. Often such individuals have other oral symptoms without a cause, such as a burning sensation of the mouth and the symptom of xerostomia without features of oral dryness.

Various medications can give rise to an abnormal taste – patients sometimes complaining of a metallic or salty taste. The most commonly implicated agents appear to be antirheumatic, cytotoxic agents, captopril and penicillamine, although the commonly prescribed metronidazole frequently gives rise to a metallic taste. A summary of the drugs that give rise to dysgeusia is provided in Table 2.

Management

The management of dysgeusia principally entails improving oral hygiene, resolving any acute gingival or periodontal disease and lessening the risk of further similar disease.

Antibacterial mouthrinses containing chlorhexidine or triclosan, or oil-water-based preparations will further lessen the risk of gingival and/or periodontal disease.

Long-standing xerostomia should also be managed.

Patients with non-oral sources of dysgeusia, or without an obvious cause of dysgeusia, should be managed by appropriate specialists. There is little evidence that zinc or copper supplementation will

lessen idiopathic xerostomia, thus the majority of affected patients should be assessed, and when appropriate, managed by specialists of clinical psychology or psychiatry.

Prognosis

Most patients with dysgeusia have resolution of symptoms when the cause is identified and corrected. Patients with idiopathic dysgeusia will also generally have resolution of symptoms – often spontaneously – although some will require clinical psychology or psychiatry management.

Table 1. Reported causes of dysgeusia

Common causes
Orodental infection
Upper respiratory tract infection
Sinus infection
Less common
Idiopathic dysgeusia
Mental illness (e.g. depression)
Drugs (see Table 2)
Uncommon
Neurological
Stroke
Head trauma (e.g. fractures of the petrous temporal bone)
Cranial nerve disorders e.g. damage to the chorda tympani during middle ear surgery
Carotid artery dissection with involvement of the chorda tympani
Facial nerve palsy
Multiple sclerosis
Borrelia burgdorferi associated - neuropathy
Gastrointestinal
Irradiation of the head and neck
Gastrointestinal reflux disease
Hepatitis and hepatic cirrhosis
Malabsorption (e.g. cystic fibrosis)
Crohn's disease
Others
Diabetes mellitus
Niacin (vitamin B3) deficiency
Zinc deficiency
Copper deficiency
Mercury poisoning

Table 2. Medications associated with altered taste

Antirheumatic agents
Penicillamine, levamisole, gold, levodopa
Antithyroid agents
Carbimazole, thiouracil
Anti-inflammatory agents
Phenylbutazone, acetylsalicylic acid
Anti diabetic drugs
Biguanides
Cytotoxic agents
Doxorubicin, methotrexate, vincristine, carmustine
Diuretics and antihypertensive agents
Captopril, diazoxide, ethacrynic acid
Antimicrobials
Metronidazole, lincomycin, ethambutol
HIV protease inhibitors
Amphotericin
Anti-seizure agents

Carbamazepine, baclofen
Others
Phenindione, allopurinol, vitamin D, oral contraceptive pill

Table 3 Clinical assessment of dysgeusia

The clinical assessment of a patient complaining of dysgeusia includes:
History of present complaint
In particular:
duration
site
initiating, precipitating and relieving factors
associated oral symptoms (e.g. burning sensation, oral dryness)
Social history
In particular:
social aspects likely to increase psychological stress
Medical history
In particular:
disease associated with xerostomia
drug history
upper respiratory tract infection(s)
Clinical examination
In particular:
cervical lymphadenopathy
salivary gland enlargement
assessment of oral hygiene, gingival and periodontal inflammation
features of long-standing xerostomia
*Additional investigations**
Usually requires referral to appropriate specialists – e.g. otorhinolaryngology, rheumatology, gastroenterology, clinical psychology.
*There is rarely any need to undertake detailed laboratory investigations in the Oral Medicine setting.

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Links

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EPIDERMOLYSIS BULLOSA

Definition

Epidermolysis bullosa (EB) is a term used to describe a group of rare mainly hereditary, chronic, non-inflammatory diseases of skin and mucous membranes. EB is characterized by the development of bullae (blisters) as a result of mild to moderate trauma. Bullae easily break, causing ulcerative lesions which usually heal with atrophic scarring.

The inheritance may be either autosomal dominant or recessive but there is also an acquired form. The hereditary types of epidermolysis bullosa have their onset at or within a few weeks of birth, can affect all populations and racial groups and there is no apparent predilection for males or females.

EB is classified into three main types (simplex, dystrophic and junctional) and at least 23 subtypes. The classification is based upon mode of inheritance, anatomic location and distribution of lesions and associated morbidity. There is also a rare acquired form of disease. Ten distinct genes encoding key molecular components of hemidesmosome anchoring complex and associated keratin filament network are recognized as underlying the three major forms of EB, and several sub-types of Epidermolysis Bullosa Simplex.

Epıdermolysıs Bullosa Sımplex

Epidermolysis Bullosa Simplex (EBS) is usually autosomal dominant, but in some cases it can be autosomal recessive. The cleavage through basal keratinocytes, which is special for EBS, is caused by mutations of genes encoding keratins 5 and 14 and plectin. EBS is characterized by lysis of basal keratinocytes, leading to the formation of intraepidermal blisters. Mainly the suprabasal layers are not disturbed, so the terminal differentiation is normal. Vesicles and bullae usually form secondary to minor trauma, friction sweating or increased body temperature. Lesions typically heal without scaring. EBS presents most commonly in early infancy, and although usually not life threatening, sometimes can be fatal.

There are 3 major subtypes of EBS:

Dowling-Meara EBS

Weber-Cockayne EBS

Köbner EBS

Dowling-Meara Epidermolysis Bullosa (EBS-DM), is not usually immediately life-threatening, but is the most severe form of EBS and it can be fatal during infancy usually because of sepsis. Extreme blistering of the skin and mucous membranes is herpetiform with marginal spreading. Other features may include nail dystrophy, milia formation and progressive palmar-plantar hyperkeratosis.

Weber-Cockayne Epidermolysis Bullosa (EBS-WC) is the mildest and the most common form of EBS. Blistering usually begins between infancy and early childhood; but in rare cases it appears

during adolescence. Blistering is primarily restricted to the hands and feet, while oral involvement is uncommon.

Köbner Epidermolysis Bullosa is seasonal milder blistering of the palms and soles, and at other sites of friction.

Dystrophıc Epıdermolysıs Bullosa

Dystropic Epıdermolysıs Bullosa (DEB) is associated with mutations in the genes encoding type VII collagen. DEB has two subtypes - *recessive epidermolysis bullosa* and *dominant epidermolysis bullosa.* The incidence of recessive DEB is approximately 1 in 300.000 births and dominant DEB 1 in 50.000.

The recessive dystrophic subtype of EB with generalized involvement is a dermatological condition producing serious mucosal lesions with sub-lamina dura separation, due to blistering below the lamina densa of basement membrane zone. There are widespread blisters involving skin and mucosa, that heal with scarring, causing dysphagia, oesophageal strictures and ocular lesions. The lesions tend to heal with fibrosis. Macroscopically, the oral mucosa, including palate and gingiva, appears smooth, erythematous and edematous. Normal growth can be a problem in children with recessive DEB, mainly because of feeding difficulties. Children with recessive DEB can show retarded skeletal growth and development affecting also the cranio-facial bones, while teeth are relatively unaffected, although the reduced jaw size can lead to severe anterior crowding.

Junctıonal Epıdermolysıs Bullosa

The junctionalis form of EB (EBJ) is characterized by separation within the basement membrane. EBJ has been linked with mutations in genes encoding for laminin 5 (alternatively known as nicein or kalinin), $\alpha_6\beta_4$-integrin and type XVII collagen. Almost all patients with EBJ present with enamel defects (including pitting, furrowing and hypoplasia), whereas the prevalance of defects in simplex and dystrophic types is similar to that of control population (~27%).

Epıdermolysıs Bullosa Acquısıta

Epidermolysis bullosa acquisita (EBA) is an acquired chronic subepidermal blistering disease that occurs primarily in adults, though an increasing number of childhood EBA has been reported over the last few years.

The aetiology of EBA is unknown, but evidence suggests the presence of autoantibodies to type VII collagen, localized to anchoring fibrils within the dermoepidermal junction of skin. Patients with EBA have IgG deposits within the dermal-epidermal junction of their skin.

EBA has two variants - *mechanobullous* and *inflammatory.* The mechanobullous variant, or *classical* EBA, is characterized by skin fragility, blisters and erosions localized to mechanically stressed surfaces, which heal with scarring and milia formation. Inflammatory variants mimic cicatricial pemphigoid, bullous pemphigoid or linear IgA disease.

Clinically, the oral lesions of EBA are similar to those seen in hereditary EBD. The most characteristic feature is soft tissue fragility with subsequent development of blistering. Blisters,

erosions, ulcerations and scarring have been described on buccal mucosa, tongue, gingival, palate and lips and it has been suggested that either perioral or intraoral blistering can lead to microstomia, ankyloglossia, scar formation and obliteration of the oral vestibular area. Patients usually have erosions and scars of the mouth, conjunctiva, upper oeosophagus, anus and urogenital tract.
The presence of scars secondary to blistering is a major diagnostic feature to distinguish EBA from bullous pemphigoid

Clınıcal presentations of EB

Bullae can be initiated on skin or mucous membranes at sites of trauma or pressure (Nikolsky's sign) and on rupturing they leave a painful erosion which heals with scar formation. Bullae can occasionally develop spontaneously. Fingers are destroyed with resorption of phalanges, and hands become unsightly and club-shaped (Fig. 1). This disorder is often associated with extracutaneus complications such as nutritional deficiencies, recurrent infections and motor disabilities. Nutritional problems are the consequence of restricted nutritional intake, chronic constipation and increased whole-body protein turnover, probably caused by chronic non-healing wounds and infections.
Oral mucosal scarring and contracture due to minor trauma such as toothbrushing, can lead to tongue-tie, obliteration of the sulci, limited opening, lingual depapillation and atrophy of the palatal folds (Fig. 3-5). During blistering and subsequent cicatrization, epithelial cells become entrapped and give rise to milium cysts, particularly in the hard palatal mucosa. Areas of leukoplakia and oral squamous cell carcinoma (OSCC) have also been reported, affecting mainly the lingual mucosa.
All three main types of EB produce oral defects. Abnormal enamel development is a common feature, including thin enamel and localized or generalized hypoplasia. Structural abnormalities include fine or coarse pitting defects, or thin or uneven enamel which may also lack prismatic structure. The amelodentinal junction may also be smooth. The mineral and chemical composition of dental enamel in EB however, is no different from normal and does not predispose the teeth to caries, although the prevalance of dental caries is significantly increased in individuals with junctional EB and recessive EB, probably due to lack of oral cleansing. There is no direct relationship between the extent of oral blistering and caries experience. The salivary flow rate has been investigated and no difference found between EB individuals and controls.

Dıagnosıs

The evaluation of any patient suspected of having EB should begin with a detailed history, including mapping of the family pedigree. A typical history includes spontaneous blister formation in areas of frequent trauma from birth or early infancy. Nonmolecular laboratory tests for the diagnosis include transmission electron microscopy (TEM), immunofluorescence antigen mapping

and immunohistochemical staining with EB-specific monoclonal antibodies. With advances in molecular biology, the underlying gene defects and linkage of various forms of EB with certain genes provide a basis for direct mutation detection and indirect linkage analysis in affected families. First-trimester prenatal diagnosis using DNA from chorionic villi and amniotic fluid can provide the diagnosis as early as 10 weeks gestation. Direct methods include Southern blotting and restriction enzyme analysis, allele-specific hybridization and polymerase chain reaction amplification. Indirect methods include DNA polymorphism.

Treatment

There is no specific therapy for EB. Traditionally, treatment has been both supportive and preventive. Common strategies include wound management, nutritional support, infection control and patient education. Topical steroids, and topical antibiotics frequently are used to promote healing and prevent secondary infection of blisters. Oral tetracycline therapy may be beneficial for patients with EBS. Dapsone and low-dose prednisolone appear to be very effective in EBA.
Performing oral hygiene is difficult because of the poor ability to grip and hold a toothbrush. Children with EB should be actively encouraged to use fluoride supplements and 0.2% chlorhexidine gluconate either as a mouth rinse or a spray.
Retention of the teeth by preventive measures is essential as dentures cannot be tolerated or even retained. Patients with EB should be seen on a regular basis to reduce bacterial plaque accumulation. Periodic follow-ups are also necessary due to the potential for malignant transformation.

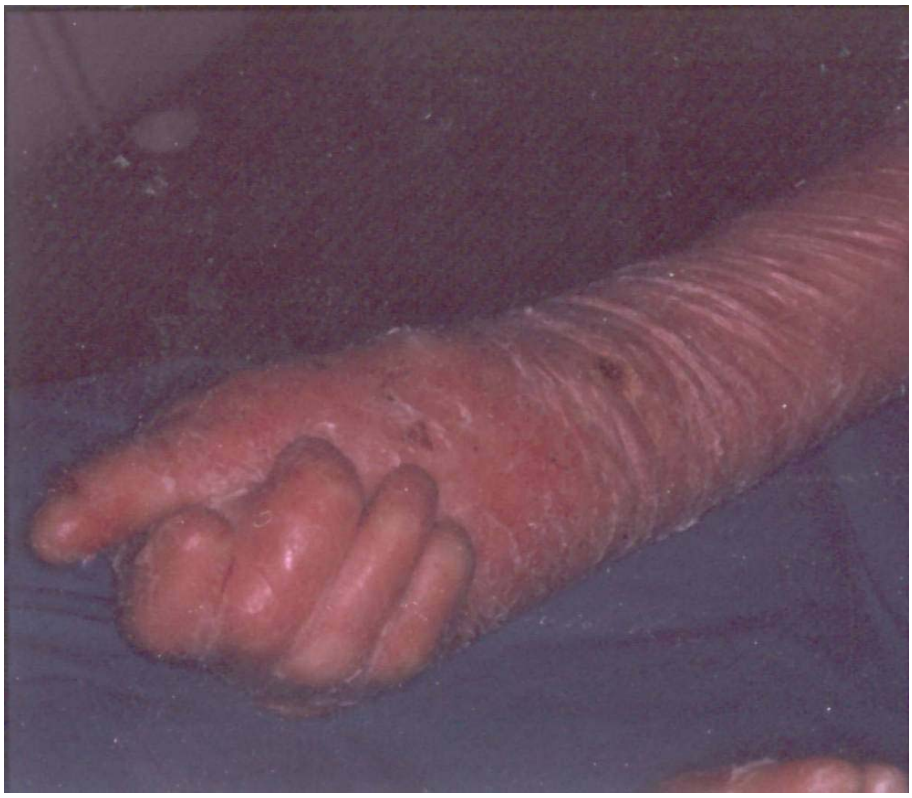

Figure 1. Epidermolysis bullosa. Cutaneous lesions

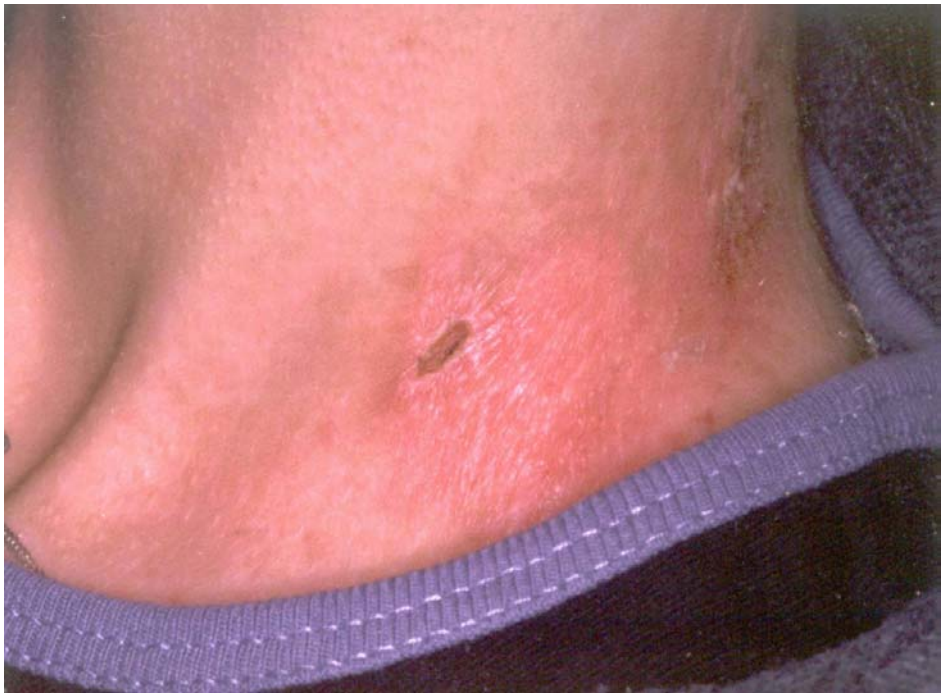

Figure 2. Epidermolysis bullosa. Cutaneous lesions

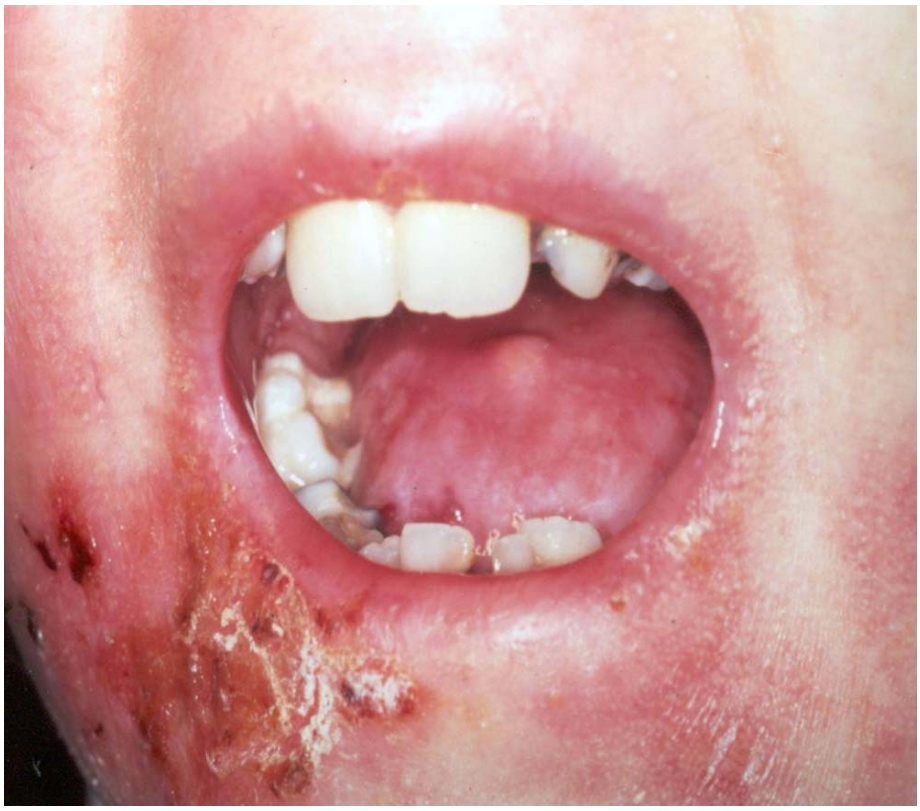

Figure 3. Epidermolysis bullosa. Oral lesions

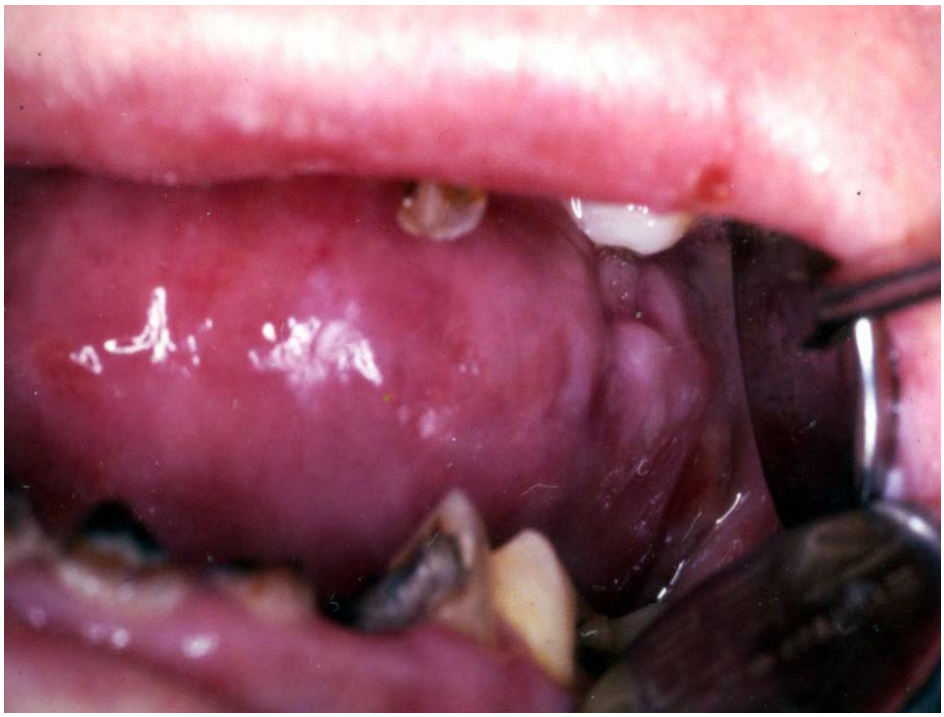

Figure 4. Epidermolysis bullosa. Oral lesions

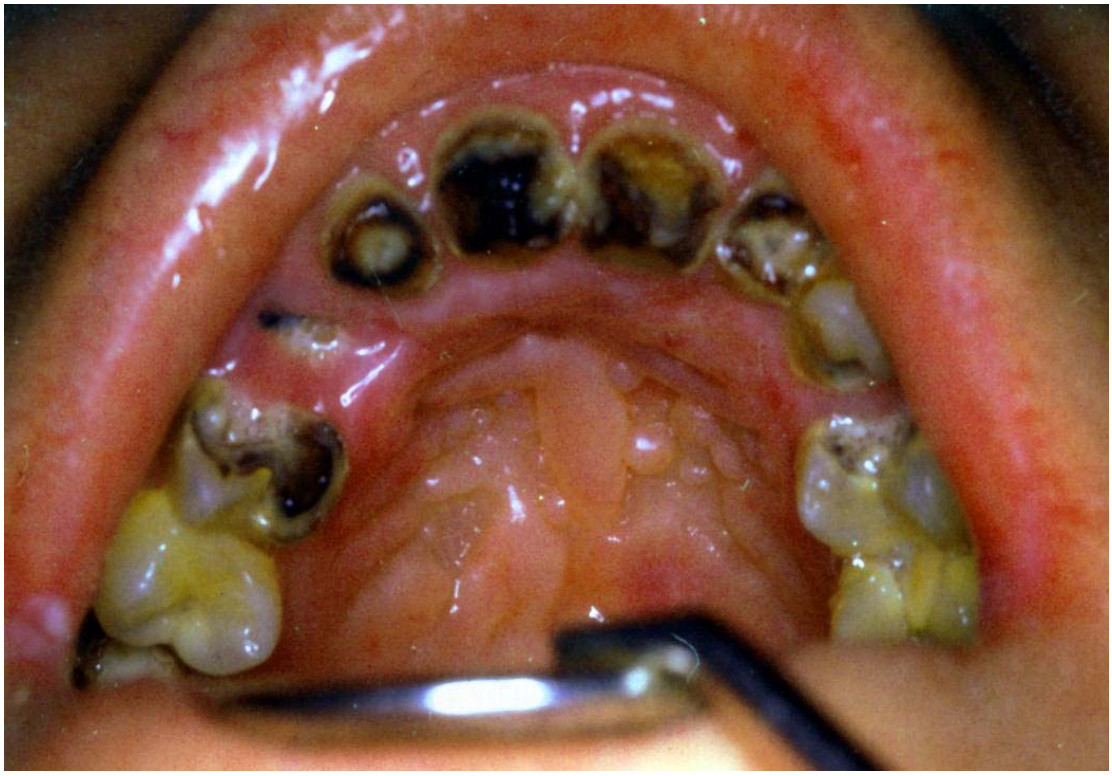

Figure 3. Epidermolysis bullosa. Palatal lesions and neglected mouth

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ERYTHEMA MULTIFORME

Definition

Erythema multiforme (EM) is an acute inflammatory disorder, usually self-limiting and often recurrent. The term EM includes a wide range of clinical presentations: a form with oral involvement only (oral EM), a mucocutaneous forms of various severity, with one or more mucosal localizations (EM minor, EM major, Stevens-Johnson syndrome [SJS]), and forms affecting large areas of the body surface (toxic epidermal necrolysis [TEN]). Currently there is no agreement over the classification of the “EM spectrum” and often the different clinical forms show overlapping features.

Epidemiology

Young adults, from 20 to 40, are most commonly affected, although children over 3 years and teenagers, represent 20% of cases. The estimated incidence ranges from 1.1 person every 1.000.000 per year in Germany, to 3.7 in the USA and up to 5-10 in Sweden.
Recurrences are seen in 37% of the cases, often characterized by a progressive worsening of the attacks. A genetic predisposition linked to HLA-DQB1*0301 allele has been reported.

Clinical presentation

Prodromal features such as malaise, fever, cephalgia, and oro-pharyngeal burning, can precede epithelial lesions by 7-10 days. The episodes of EM are usually acute, self-limited and recurring, and often preceded by systemic symptoms such as malaise, fever, headache.The classic skin lesion of EM is the “target” or “iris” lesion, which consist of concentric erythematous rings separated by skin of near-normal appearance; the tissue in the centre of the target may be erythematous or tan. These lesions disappear in about 1-4 weeks leaving a transiently hyperchromic skin. Extremities, especially extensor surfaces as palms and soles, are typically involved, usually with a symmetric distribution, whereas face, neck and trunk are less commonly involved.
In EM major, skin lesions usually follow mucosal lesions; they may resemble classical target skin lesions, but are often characterized by bullae and erosions which can cause epidermal loss. The early skin lesions of toxic epidermal necrolysis (TEN) (macules with a central darker area) can simulate the classical ones of EM, but they show an irregular edge and lack the oedematous ring. The lesions of EM affect the face, limbs and trunk. The disease can also start with a severe diffuse erythema; quickly evolving into large flaccid blisters, resulting in a massive epidermal loss.
Early oral EM presents erythematous spots which progress to blisters that quickly break, resulting in erosion and/or ulcers. Oral involvement varies from a few aphthous-like lesions to multiple, superficial, widespread erosions. Lesions are irregular but well demarcated, sometimes

associated with pseudomembranes or crusting. The reported incidence of oral lesions in EM varies considerably, ranging from 25 to 70%, but several authors have reported exclusive intraoral lesions in EM patients. Any area of the mouth may be involved, especially the lips and the anterior part of the oral cavity (tongue and buccal mucosa); gingival involvement can also be seen. Symptoms range from mild discomfort to severe pain that can leave patients unable to open the mouth, to speak or to eat.
The mucosal involvement in EM major and TEN, is early and constant, affecting the oral cavity (95-100% of the cases), eyes (70-75%), genitalia (60-65%) and occasionally pharynx, larynx, oesophagus and respiratory tract.

Aetiopathogenesis

Although many factors may be involved in the EM, often the basic cause of the disease is unknown. In contrast to skin EM, which is mostly caused by systemic drugs (principally anticonvulsants, sulfonamides, non-steroidal anti-inflammatory drugs and antibiotics) and herpes simplex virus (HSV) infection, the aetiologic agents remain obscure in many oral EM cases. Many studies from dermatological clinics, based on cohorts with cutaneous involvement, found a relation between EM and HSV infection which has not always confirmed in studies of stomatological cohorts. HSV-DNA has been demonstrated in cutaneous and oral lesions, but the role of HSV in the aetiology of oral EM remains uncertain.

Diagnosis

Since there are no specific markers for EM, the diagnosis is based mainly on the clinical features and history.
All the patients referred to a stomatological clinic should also have a dermatological examination (including genitalia), in order to evaluate the presence of lesions involving the skin and/or other mucosal sites. The role of precipitating agents such as herpes infection and drugs should be established. Herpes involvement can be established by evaluating the following criteria: recurrent EM, history of recurrent herpes, recent clinical herpes (preceding EM by 3 weeks), and demonstration of a recent HSV infection (seroconversion). Drug involvement is possible if there is a chronological relationship between drug use and the eruption.
The differential diagnosis includes pemphigus vulgaris, mucous membrane pemphigoid and lichen planus (which have specific histopathological and immunopathological features), in addition it must always be considered oral primary HSV infection, characterized by frequent gingival involvement (rare in the EM). EM has no specific or consistent histological pattern. Pathological parameters can be useful for differential diagnosis in cases with an overlapping clinical aspect. Biopsies must be assessed by means of routine haematoxylin and eosin staining, to exclude any other pathology

with a similar clinical pattern but a specific histopathological one. In questionable cases, a standard direct immunofluorescence can also be performed.

Treatment

Treatment depends on the form of EM. Considering the self-limiting nature of the condition and unidentifiable aetiology in many, specific treatment is available for few patients. Systemic anti-inflammatory/immunoregulating agents seems to be the most effective treatment to control oral EM. In particular, prednisone is the most frequently used drug, sometimes associated with azathioprine. Frequently the shortness of the therapy (a full dose of prednisone for 3 days only and then taper the dose) does not require additional azathioprine. In the case of oral EM, topical corticosteroids (fluocinonide or clobetasol in adhesive base) can be useful. However, given the frequent wide extent of the oral lesions and the high prevalence of extra-oral lesions, systemic drugs are often used.

Anti-viral drugs are justified in cases of proved HSV involvement. In SJS and TEN it is mandatory to identify and withdraw the suspected drug. Systemic corticosteroids may be used for the treatment of the SJS. TEN must be treated in a hospital able to manage scalded patients. There is no agreement on the usefulness of high doses of systemic corticosteroids or the effectiveness of other treatment, such as plasmapheresis, hyperbaric oxygen therapy or other immunomodulating drugs such as azathioprine, cyclophosphamide, ciclosporin or high-dose intravenous immunoglobulins.

Prognosis and complication

In case of severe SJS or TEN the mortality rate ranges from 10% to 30%. In cases of oral EM, EM minor and moderate SJS, appropriate therapy generally gives a complete resolution within 10-15 days.

Prevention

There are no means to reliably prevent EM episodes nor recurrences. Some authors suggest the prophylactic use of an antiviral agent such as aciclovir in patients with oral recurrent EM with a putative viral cause. However there are insufficient data to support this. It is important to remember that drug use can cause a wide range of EM manifestations. For this reason, at the first episode of EM it is imperative to look for any drug that could be responsible, in order to avoid future administration - since the severity of the manifestations often increases in further episodes and in case of severe SJS or TEN this could be lethal.

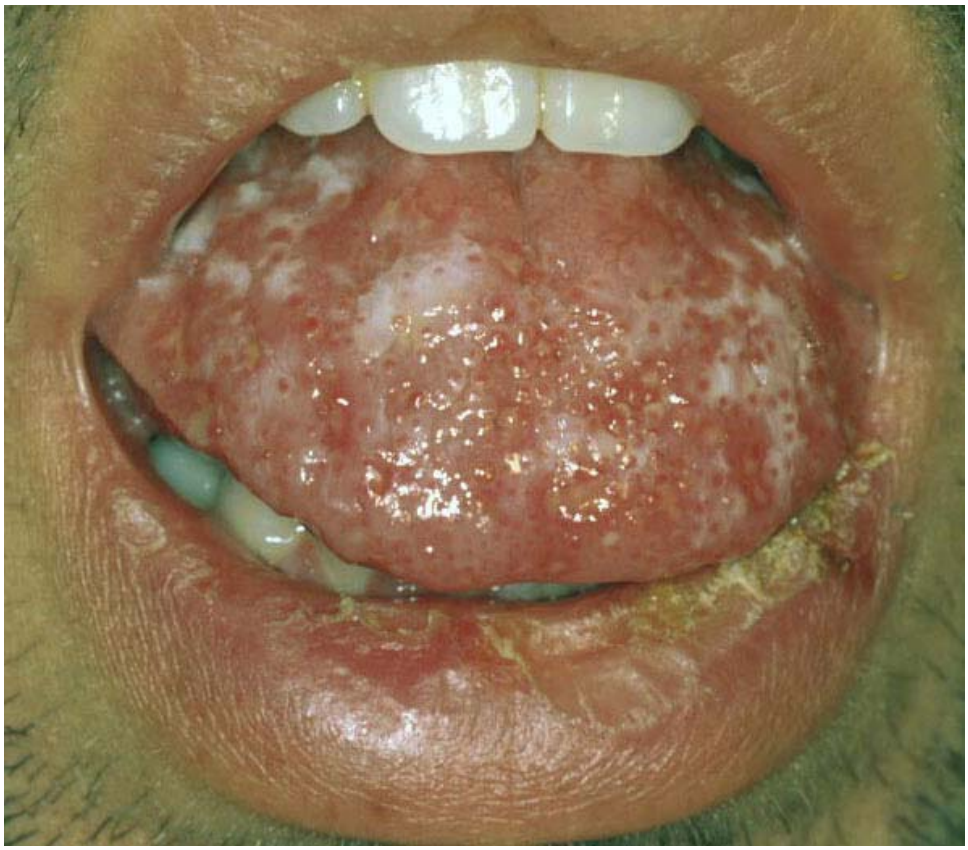

Figure 1. Erythema multiforme: oral and labial lesions

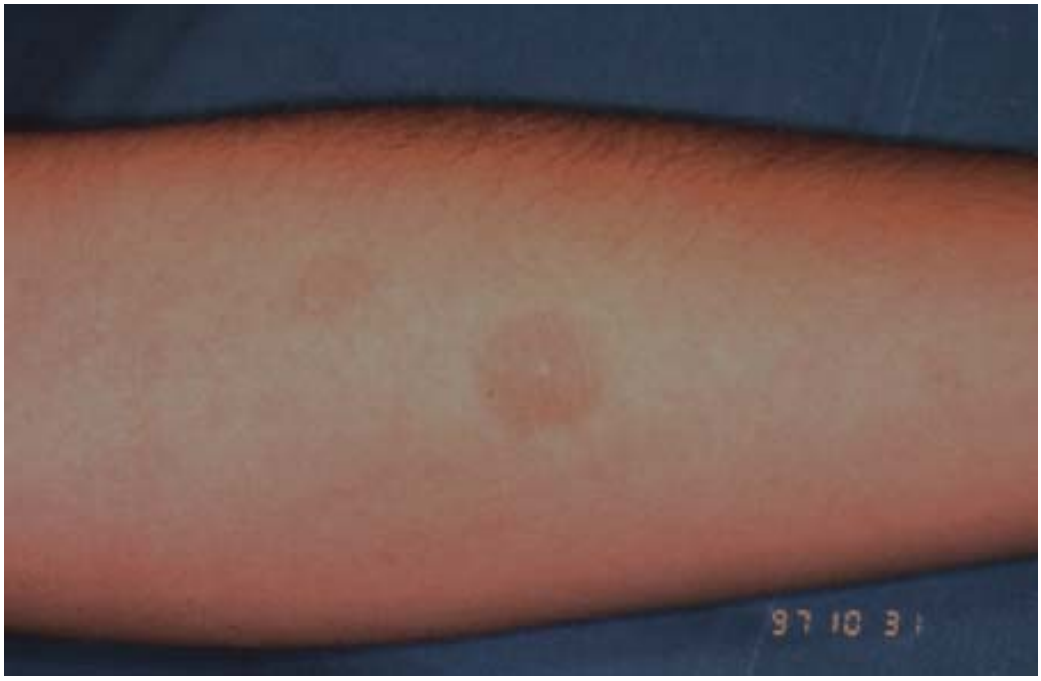

Figure 2. Erythema multiforme: cutaneous lesions

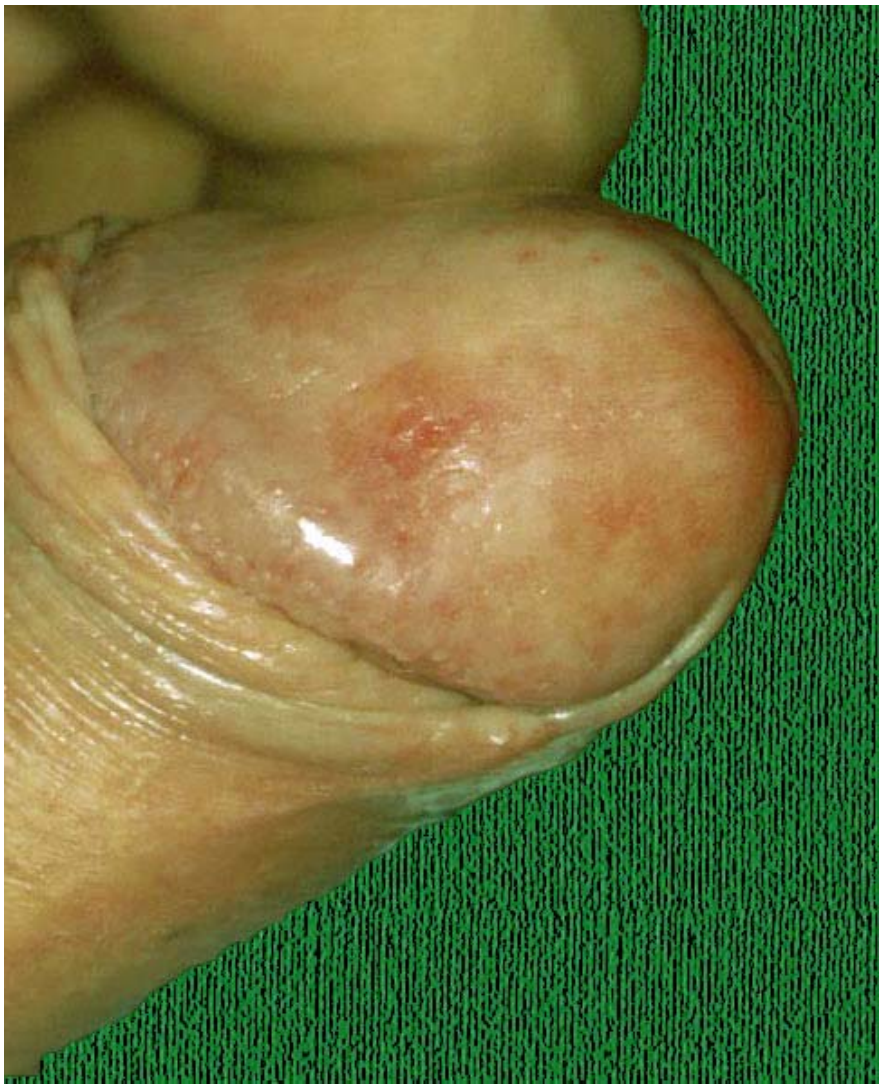

Figure 3. Erythema multiforme: genital lesions

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GEOGRAPHIC TONGUE

Definition

Geographic tongue is a fairly common, usually painless inflammatory disorder that affects mainly the dorsum of the tongue. The pattern of the lesions give the surface of the tongue the appearance of a map, hence the term «geographic». Since the first description in 1831, other terms related to this condition have been: benign migratory glossitis, glossitis areata migrans, wandering rash of the tongue, erythema migrans, stomatitis and erythema areata migrans. As no risks or consequences have been associated with this condition, the term benign should be accepted for this disorder.

Epidemiology

Geographic tongue occurs in approximately 3% of the population worldwide. In epidemiological reports the prevalence of the condition varies between 0.28% and 14.4% in all age groups, although it occurs more commonly in adults than in children. Females are affected twice as often as males. There is no apparent racial or ethnic predilection.

Clinical presentation

Geographic tongue presents with one or more irregular, well-defined red areas, most commonly surrounded by a raised white-greyish margin on the dorsum and/or borders of the tongue. The smooth red patches can have various shapes and size and are due to a localized desquamation with loss of tongue filiform papillae. The tongue papillae appear hyperkeratotic in the margins of the red denuded lesions, while fungiform and other tongue papillae are unaffected. Usually, the lesions persist for a short period in one area, disappear within a few days, and then recur in another area with no apparent reason. The disease is characterized by periods of exacerbation and remission, during which lesions heal without residual scar formation. These may last days, months, or years. Continuously changing patterns and migration of lesions on the tongue surface with unusual appearance of the tongue are the main complaint. Patients usually refer no painful symptoms nor taste loss, but slight irritation to increased sensitivity in the affected areas are sometimes reported, particularly with salty, spicy and acidic foods.

Geographic tongue is often associated with fissured tongue, although the cause is still unknown. Very rarely, circinate red areas with whitish borders similar to the typical tongue lesions can occur in other areas of the mouth mucosa, mainly in the labial vestibular and buccal mucosa. In this cases the condition is best defined as geographic stomatitis.

Etiopathogenesis

The cause of geographic tongue is unknown, but a strong familiarity has been reported. A polygenic inheritance and the association with a number of other genetic or medical conditions has been suggested. In particular, an increased frequency is observed in patients with psoriasis; otherwise the great majority of those with geographic tongue do not develop psoriasis. Moreover these two conditions share histopathologic similarities. Inflammation characterizes the histology of the red depapillated areas of geographic tongue with loss of keratin, neutrophils, lymphocyte and plasma cells infiltrate and intraepithelial microabscesses.

Geographic tongue is not an infectious disease nor it is related to systemic infections like HIV. It is not transmissible between partners.

It is not linked to the use of tobacco but it has been reported as a rare side effect of lithium treatment.

Geographic tongue is more common in people with allergic diseases such as atopy, asthma, eczema and contact allergy but a clear pathogenic link with allergy has not been actually demonstrated.

Hypersensitivity to dental materials may contribute to the ethiology or the exacerbations of the condition, but no definitive evidences are available.

Precipitating factors that stimulate lesion formation and/or subjective complaints include stress, gastric diseases, alcoholic beverages, salty, spicy and acidic foods, and other local irritants such as some ingredients of toothpastes.

The observed effect of oral contraceptives in young women on the lesions of geographic tongue suggested a role for hormone levels in the expression of the condition.

Diagnosis

Diagnosis of geographic tongue is based on the clinical aspect of lesions and patient history and seldom requires histologic confirmation. Geographic tongue should be differentiated from candidiasis, leukoplakia, contact allergy, lichen planus, lupus erythematosus and trauma. Once the diagnosis is made, the patient should be informed about causative factors, the course of the condition and its benign nature.

Treatment

When asymptomatic, geographic tongue requires no treatment. Anxious and cancerophobic patients should be treated with reassurance and local measures. Several treatments have been suggested in symptomatic patients. Oral hygiene and mild mouthrinses should help in cleaning the mucosal surfaces and reducing the discomfort. Topical retinoids are the most

successful but have transient effect. Topical anaesthetics, topical corticosteroids, antihystamines and antifungals may be used to alleviate burning symptoms.
A very few patients with geographic tongue are zinc deficient; if low zinc levels are demonstrated, zinc supplementation should help.

Prognosis and complications

Geographic tongue is a benign condition that never turns into malignancy. There are also no reported consequences nor risks associated with this condition. The only complication is the discomfort due to the persistent clinical appearance and frequent reccurence after healing. The reported association between geographic tongue and allergic diseases could sometimes suggest the dental practitioner should obtain medical advice for the affected patient.

Prevention

As the cause is unknown, the condition is not preventable. However it is advisable to promote optimal oral hygiene and avoid contact with local factors that could precipitate symptoms, such as spicy and acidic foods, alcohol, irritants in toothpastes and mouthrinses.

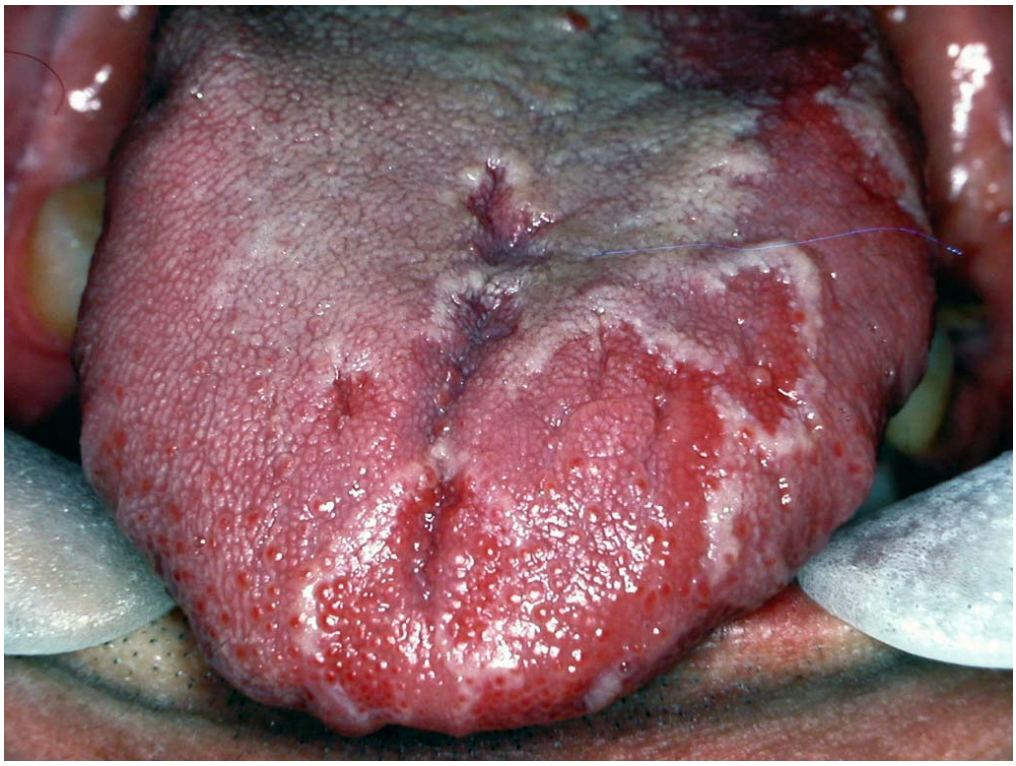

Figure 1. Clinical appearance of a geographic tongue with denuded areas delimited by hyperkeratotic borders

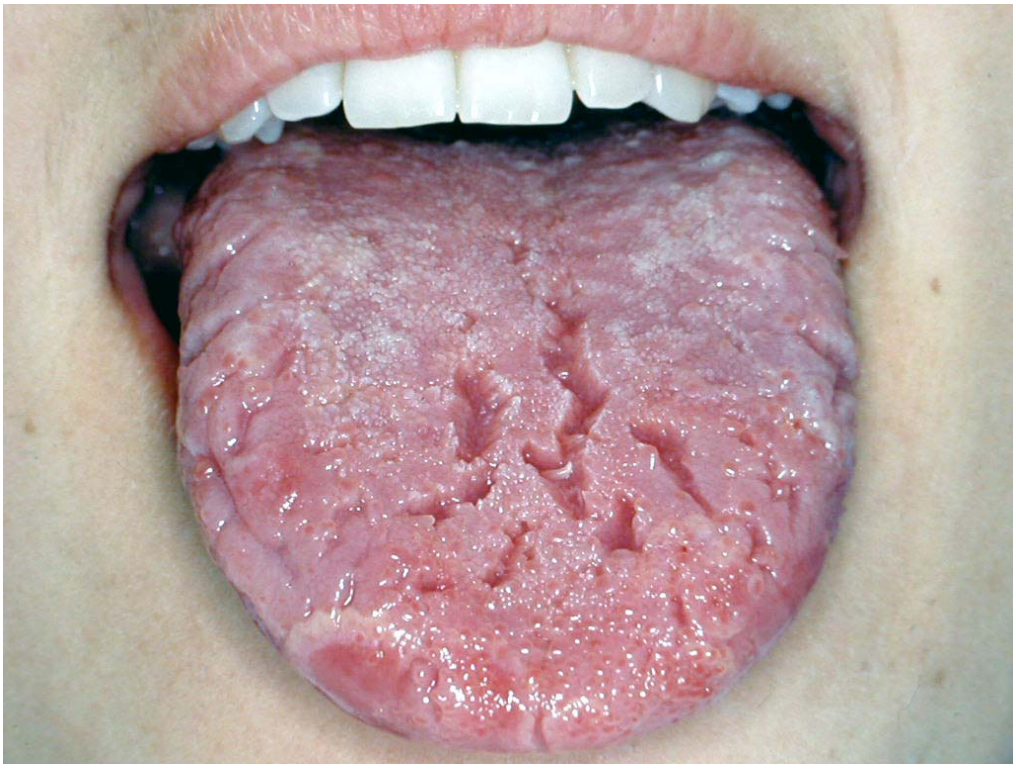

Figure 2. geographic tongue associated with fissures of the dorsum

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http://www.usc.edu/hsc/dental/opath/cards/geographic tongue.html

http://www.emedicine.com/derm/topic664.html

GRAFT VERSUS HOST DISEASE

Definition

Graft-versus-host disease (GVHD) is the most common complication of allogeneic hematopoietic stem cell transplantation (HSCT). In HSCT, the patient's bone marrow is destroyed with chemotherapy and/or radiation and replaced by donor hematopoietic stem cells. In allogeneic HSCT the donor is usually a close family member or occasionally someone outside the family who has been found to be a "match".

GVHD occurs when transplanted donor's immune cells (graft) react to patient's tissues (host) and tries to destroy them. As a consequence of this action, the patient's organs impair their ability to function, and increase the patient's susceptibility to infection.

GVHD is generally divided into two syndromes - acute and chronic. Acute GVHD (aGVHD), is that occurring within three months after transplantation, and chronic GVHD (cGVHD), usually develops after the third month post-HSCT. Patients may develop one, both or neither reaction.

Acute and chronic GVHD differ in their symptoms, clinical signs and time of onset. Acute GVHD primarily involves the skin, liver, oral mucosa, and gastrointestinal tract. In contrast, cGVHD presents a far more varied clinical picture including liver dysfunction, pulmonary fibrosis, sclerodermatous skin changes, oral and gastrointestinal mucosa changes, and a reduced production of tears and saliva.

Epidemiology

The incidence of GVHD varies considerably according to immunologic risk factors such as degree of histocompatibility transplantation antigen disparity between donor and recipient, age of recipient and donor, sex and parity of donor, type of GVHD prophylaxis, and history of recipient herpes virus infection. The range of incidence of acute GVHD is 30% to 75% and of chronic GVHD is 25% to 70%.

With the lack of clearly defined criteria for diagnosing *oral* aGVHD, it has not been possible to accurately determine the incidence rates. Oral involvement occurs in 80% of patients suffering from cGVHD and the oral cavity may, in some instances, be the primary or even the only site of cGVHD involvement.

Clinical presentation

Because of the several potential causes of oral mucosal changes during the first period post HSCT, it is difficult to distinguish changes due to aGVHD from those due to other conditions (i.e. mucositis). The majority of reports have attributed to aGVHD punctate or generalized mucosal erythema, white striae or papules on the oral mucosa and lips (in patterns similar to

those seen in oral lichen planus), mucosal erosion-desquamation-ulceration, xerostomia, and pain. However, many of these changes can also be caused by pre HSCT chemoradiotherapy conditioning, post-HSCT drugs, or infections.
Generally, the oral manifestations of cGVHD are clinically similar to those of aGVHD, although in the case of the former they may be more readily recognized with the resolution of conditioning-regimen oral toxic effects and decreased risk of oral infections.
Lichen planus-like lesions are the most distinctive oral change of cGVHD: hyperkeratotic striae, patches, plaques, and papules may affect oral and perioral tissues and severe atrophy and ulcerations, resembling erosive lichen planus, can be noted in patients with severe extensive cGVHD. The ulcerations are often covered with a heavy pseudomembranous clot that is grayish white to yellowish. In addition, mucosal surfaces appear erythematous and atrophic, aspects attributed to a relative loss of keratinization or loss of surface structures as filiform papaillae or gingival stippling. Oral pain is often reported by patients with cGVHD and is either continuous or elicited by eating, drinking or oral hygiene procedures.
Patients with cGVHD usually experience xerostomia resulting in subjective suffering and disturbances in chewing, swallowing and speaking, along with increased levels of dental caries and oral candidiasis.

Aetiopathogenesis

GVHD occurs when donor graft T cells recognize antigenic disparities between donor and recipient tissues. T cells are special white blood cells that are able to recognize foreign matter in the body. Usually, T cells orchestrate attacks on bacteria, viruses and other foreign substances. They can also distinguish "self" from "non-self" human cells. In fact, on the surface of many human cells there is an inherited set of genetic markers called "human leukocyte antigens" (HLA). Like a fingerprint, no two persons' set of HLA markers are exactly the same (except for identical twins). The T cells use these HLA markers to distinguish "self" from "non-self." If a "non self" human cell is encountered in the body, the T cells quickly activate the immune system to destroy it. Greater is disparity between the foreign organ's HLA markers or "tissue type" and that of the T cells, swifter and more vigorous will be the attack. Based on this mechanism, T cells can induce rejection of a transplant organ such as liver or kidney. The ability of the immune system's T cells to distinguish "self" from "non self" can create a serious problem after allogeneic HSCT. In this case, the transplanted organ are the T cells; as a consequence, the donor's T cells may identify the patient's tissues as "non-self" and attack them. In oral GVHD the target tissue ("non self") are the oral mucosa and minor salivary glands.

Diagnosis

Currently, the diagnosis of oral GVHD depends on the demonstration of systemic signs and symptoms of GVHD and the exclusion of other causes of oral lesions.
Oral lichenoid lesions are statistically related to cGVHD. Oral lichenoid lesions in cGVHD however, cannot be distinguished either clinically or histologically from conventional oral lichen planus. A past history of HSCT is the key element to differentiate oral lichen planus from oral GVHD. Xerostomia and decreased whole saliva flow have a low specificity in the diagnosis of cGVHD and might also be caused by drugs.
Histopathologic criteria for both acute and chronic GVHD are similar, although there have been no large studies on the histopathology of oral aGVHD, since it is difficult to obtain oral biopsies during the immediate post-HSCT period, when the patient is at high risk for infections and bleeding complications.
The histopathological changes of the oral mucosa in cGHVD include epithelial atrophy, with apoptotic bodies, hydropic degeneration of the basal cells, and a mononuclear sub-epithelial cell infiltrate with lymphocyte invasion. The minor salivary glands may show periductal lymphocytic or lymphoplasmacytic infiltration of both intralobular and major excretory ducts, with more pronounced ductal damage leading to necrosis of ductal epithelium, resulting in obstruction and eventual acinar damage and fibrosis.

Treatment

Management of oral aGVHD consists of systemic treatment, pain control, and local, usually palliative, measures. In general, oral lesions of aGVHD will respond to systemic immunosuppression, and patients need opiates for pain control. For local comfort and symptomatic relief, saline rinses, topical anaesthetics such as viscous lidocaine or diclonine hydrochloride, and combinations of lidocaine and/or diphenhydramine hydrochloride can be helpful. Topical corticosteroid rinses (dexamethasone) and gels (fluocinonide, clobetasol, or triamcinolone) have been used with some success.
Management of oral cGVHD consists of appropriate systemic therapy combined with proper oral hygiene and use of topical drugs. In general, topical steroid preparations, such as flucinonide and clobetasol gel, and steroid elixirs (dexamethasone or betamethasone) are the mainstay of local treatment for cGVHD. Also immunosuppressants such as ciclosporin and azathioprine have been used as topical therapy in oral GVHD. The administration of the photosensitizing drug psoralen, followed by skin and oral exposure to ultraviolet A irradiation is successfully used in the treatment of cutaneous and oral GVHD. Some evidence suggests that patients who do not respond to systemic and/or topical steroids may benefit from the use of thalidomide. There are only isolated reports of the use of tacrolimus for cutaneous GVHD, but no data on its use in oral lesions.

In patients with xerostomia, the available treatment options, such as salivary substitutes, are largely palliative and usually offer only short-term relief. Pilocarpine, a cholinergic agonist, has been long known to stimulate salivary secretion.
Additionally, careful diagnosis and appropriate treatment can reduce the oral pain caused by superimposed oral infections due to herpes simplex virus and *Candida* species. Good oral hygiene and prevention of tissue trauma are imperative to minimize the risk of infection, pain, periodontal changes and caries. Topical fluorides are indicated in cases of severe xerostomia to prevent rampant caries.

Prognosis and complication

In patients with oral manifestation of aGVHD, oral infections, due to *Candida* species and herpes simplex virus can occur simultaneously, exacerbating the symptoms and making recognition of aGVHD more difficult. Chronic GVHD may be associated with altered or reduced taste; in this case xerostomia can have an impact on speech, deglutition, and when present, use of oral prostheses, apart dental demineralization and caries.
Moreover, oral cGVHD might be a predisposing factor in the development of oral squamous cell carcinoma.

Prevention

There are no reported clinical trials that have evaluated prevention or treatment of oral GVHD. Clearly, the best means of preventing or managing oral GVHD is the successful systemic prevention or management of systemic disease (ciclosporin, prednisone). Recommended prophylactic regimens to prevent or minimize the oral manifestations of GVHD include removal of all appliances and compromised teeth with definitive dental restoration before HSCT. In the post-HSCT period, frequent oral rinsing with weak sodium peroxide and bicarbonate solution is useful. Infections prophylaxis can be achieved with topical nystatin or azoles (*Candida*), chlorhexidine (bacteria), and aciclovir (herpes simplex).

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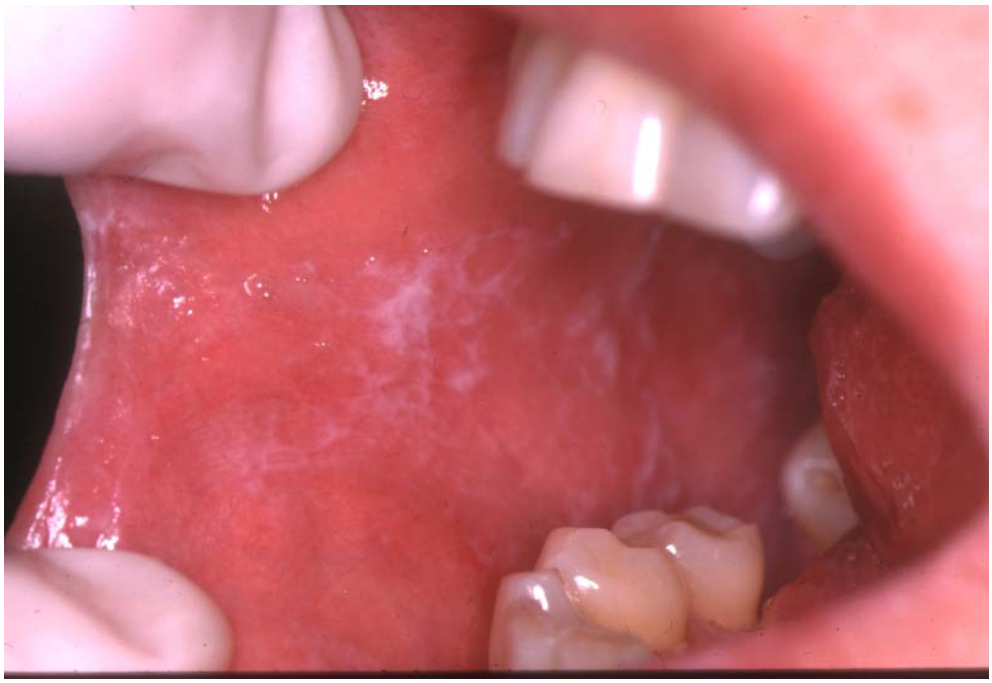

Figure 1. Oral GVHD, lesions of the oral mucosa

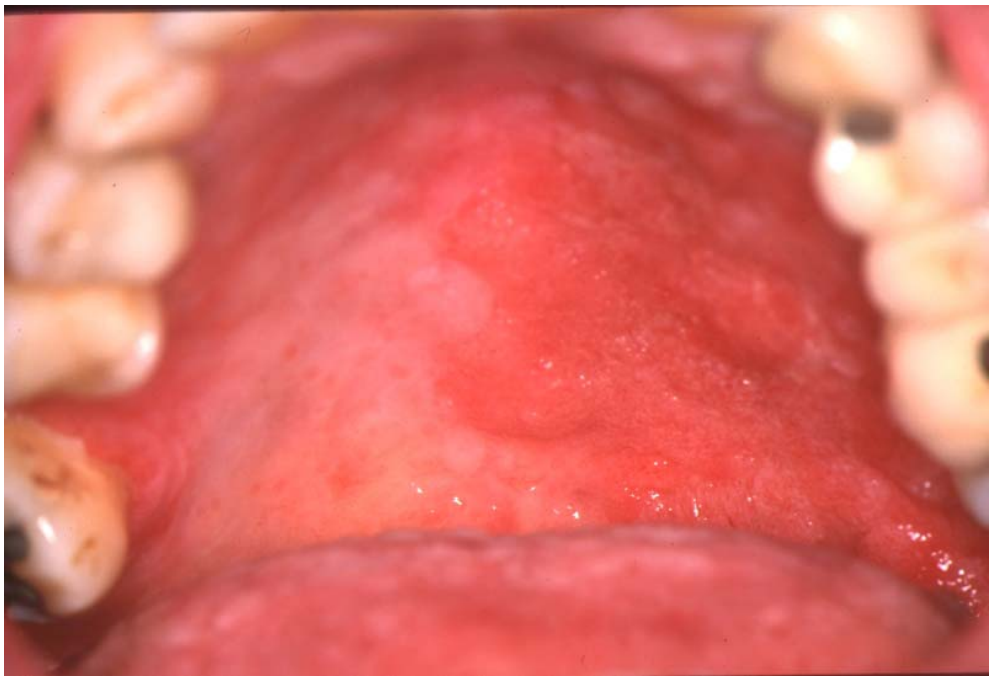

Figure 2. Oral GVHD, lesions of the palate

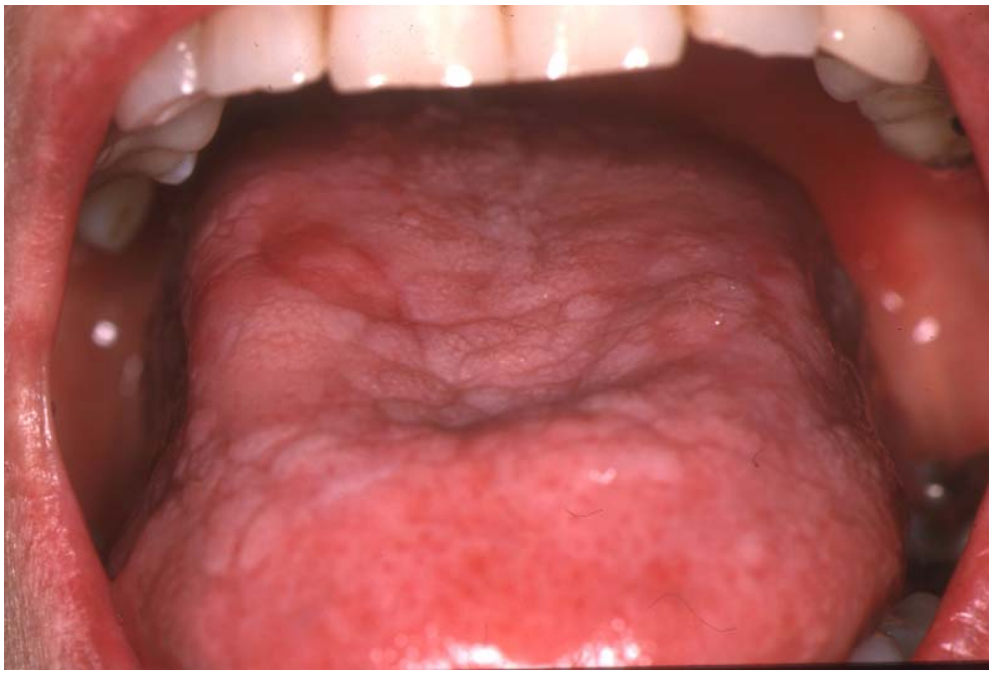

Figure 3. Oral GVHD, lesions of the tongue

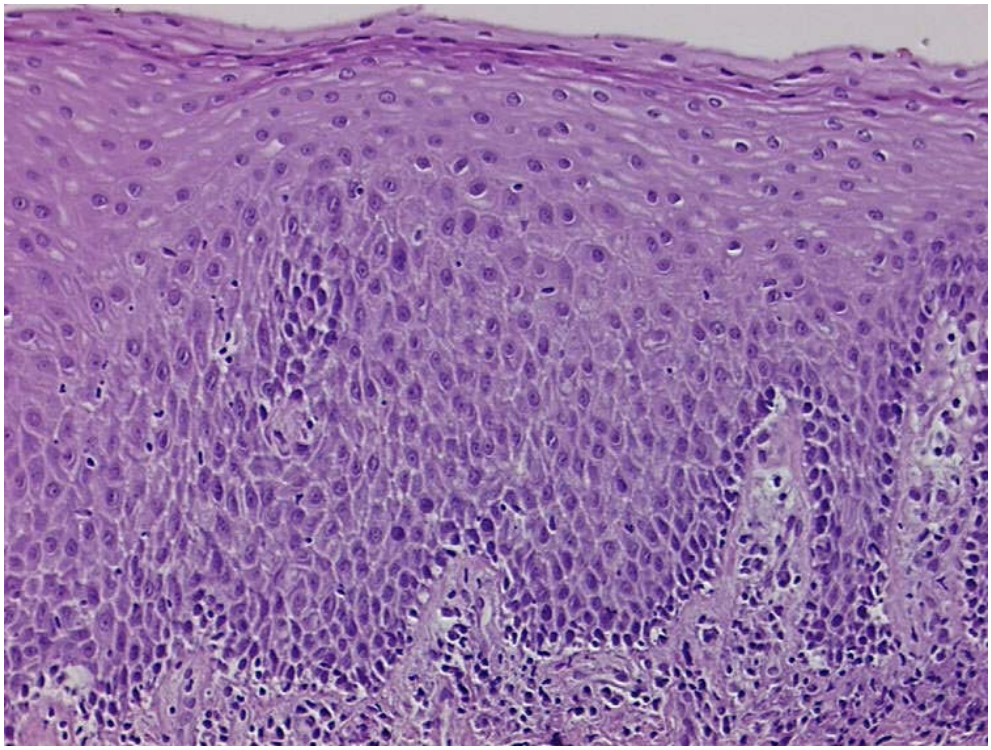

Figure 4. Oral GVHD, histological aspect

HAIRY LEUKOPLAKIA

Definition

Oral hairy leukoplakia (OHL) was first observed in 1981 and reported in 1984 as a common, benign, asymptomatic, white, non-removable lesion of the lateral borders of the tongue in patients with HIV infection and AIDS. The lesion is rare in the healthy population. In patients with HIV infection, when laboratory estimates are not available, OHL may be a useful clinical marker of the presence, severity and progression of HIV disease. Since its first description, OHL has been observed in immunodeficient patients with other causes of immunosuppression (chemotherapy, long term steroid use, organ transplantation). Thus, it is regarded as a clinical marker of impaired immune status, in general, and its appearance should prompt the clinician to carry out further investigations in order to establish the underlying cause of immunosuppression. Furthermore, OHL has an intimate etiologic relationship with Epstein-Barr virus (EBV) which replicates floridly within the lesion. Thus, in addition to its clinical significance, OHL has a unique biologic importance offering a unique in vivo research model for the study of the Epstein-Barr virus.

Epidemiology

Reported prevalence rates of OHL vary considerably according to the clinical criteria used and the characteristics of the study population such as the type of immunosuppression, risk group for acquisition of HIV disease (homosexual, hemophiliacs etc), clinical stage of the patients etc. On average, in the early periods of the HIV pandemic, it was seen in one quarter of HIV-infected patients. With the passage of time, the understanding of the pathogenesis of HIV disease was improved and new drugs were developed to combat the infection. Medication has changed from monotherapy to current triple combination therapy (Highly Active Anti-Retroviral Therapy;HAART), which resulted in a dramatic improvement of all virological and immunological parameters of the patients and subsequently to a decrease in the prevalence of HIV-associated oral lesions as compared to earlier periods. Thus, the current incidence of OHL has dropped from 25% to less than 10%. There are very few reports of the occurrence of OHL in immunocompetent subjects, but these lesions do not contain EBV.

Clinical presentation

Oral hairy leukoplakia presents as unilateral or more often bilateral, adherent, white or gray patches mainly on the lateral lingual margins and sometimes the dorsum or ventrum of the tongue. The surface of the patches has usually a corrugated appearance forming prominent folds or projections (sometimes so marked as to resemble "hairs", hence its name). When chronic, these alterations assume a more homogenous appearance similar to that of idiopathic leukoplakia. When seen at the ventral surface of the tongue, the lesion may be flat. OHL may occur (rarely) on other mucosal surfaces such as buccal mucosa, floor of the mouth and soft palate. OHL has so far not been observed in other areas than the oral. Although usually symptomless, it may cause a burning sensation, while patients may complain of its unsightly appearance, especially when it is extended on all lingual surfaces.

Aetiopathogenesis

Though the pathogenesis has yet to be elucidated in detail, its cause is currently thought to be a specific EBV infection facilitated by immunodeficiency. EBV is acquired by over 90% of the world population during childhood or adolescence and thereafter remains in a carrier state for the lifetime of the infected host. The virus is shed in saliva and cellular EBV receptors are found in the upper layers of parakeratinized oral epithelium. The close relationship between EBV infection and OHL is evident since EBV antigens have been demonstrated in tissue sections by immunohistochemical analysis and EBV-DNA has been demonstrated in tissue by molecular techniques such as Southern blotting and in situ hybridization (ISH). Intracellular herpes virus particles have also been observed by electron microscopy. Experiments have shown that the epithelial hyperplasia observed in OHL is directly related to the combined action of EBV proteins, which delay the death of the oral epithelial cells allowing very intense viral replication without themselves undergoing lysis. Extensive molecular studies have demonstrated that several EBV variants may be present within a single lesion, the infecting types may change over time, strain recombinations may also occur but whether the newly created strains lead to or are consequential to OHL is unclear. Also unclear is how OHL is initiated and whether it develops after EBV reactivation from latency state or is a result of superinfection of upper epithelial cells by the virus derived from saliva or other infected cells. Also, the mystery of why OHL is localized mainly on the lateral borders of the tongue has not been adequately clarified.

Diagnosis

Generally, the clinical features alone (as described above), the lack of response to anti-fungal therapy, combined with other signs of immune dysfunction and the social and medical history of the patient should provide clues to the provisional diagnosis of OHL. Histological examination is indicated only when clinical features are vague. Epithelial hyperplasia with hyperparakeratosis and acanthosis are consistent features of OHL together with koilocytosis with pyknotic nuclei and perinuclear halos in the prickle cell layer, intranuclear inclusions, paucity or absence of Langerhans cells and a sparse inflammatory cell infiltrate in the lamina propria. It is important to note that in many cases of OHL there may be a supervening fungal population that should not be overlooked or mistaken as oral candidosis.

However, the histologic changes are not specific to OHL, thus, the demonstration of EBV is essential to the definitive diagnosis of OHL. Demonstration of EBV in histological or cytological specimens by mean of molecular techniques or electron microscopy is needed for the definitive diagnosis of OHL. Exfoliative cytology is a useful alternative to incisional biopsy, for which there are often contraindications (e.g., patients with bleeding disorders, children, or severely debilitated patients). Although, in clinical practice, the need to definitely diagnose presumed OHL seldom arises, it is important to differentiate it from other oral lesions that may have a similar clinical appearance. Correct early diagnosis can facilitate the establishment of the underlying immunodeficiency. The differential diagnosis should include idiopathic leukoplakia, smoker's keratosis, frictional keratosis, hyperplastic candidiasis, lichen planus, lichenoid reaction etc.

Treatment

Since OHL is usually symptomless and has no known premalignant potential, treatment is seldom required. It tends to clear with HAART. Several treatment options are available for symptomatic lesions, such as topical retinoids, topical podophyllin, surgical excision and cryotherapy, but none prevent the recurrence of the lesion after therapy. Antifungal therapy may lead to some reduction in the extent of the lesion but does not eradicate the infection. Antiviral agents can result in amelioration of OHL, but lesions recur soon after discontinuation of therapy while side effects may occur and resistant viral strains may arise. Furthermore, it has been documented that OHL improves spontaneously in about 10% of the cases.

Prognosis and complication

No cases of malignant transformation in patients with preexisting OHL have been reported, although mild cellular atypia has been described. Patients might complain for its unsightly appearance, in which cases, therapeutic intervention might be indicated. OHL can be an early, if not, the first sign of HIV infection. OHL can be used as a convenient clinical marker of HIV-disease severity, since most affected patients have CD4(+) T-cells counts < 400/mm^3. In addition, OHL has a reliable prognostic value in the natural history of HIV disease. The estimated rate of progression to AIDS at one year for subjects with OHL varies from 10% to 48% and at two years from 24% to 63%. Patients with OHL are also more likely to develop lymphomas.

Prevention

Immunosuppression is a precondition for the development of OHL. HIV infection dramatically enhances the risk of its appearance, but why this is so remains puzzling. The improvement of immunological status of HIV-infected patients with the HAART therapy has dramatically reduced the frequency of OHL.

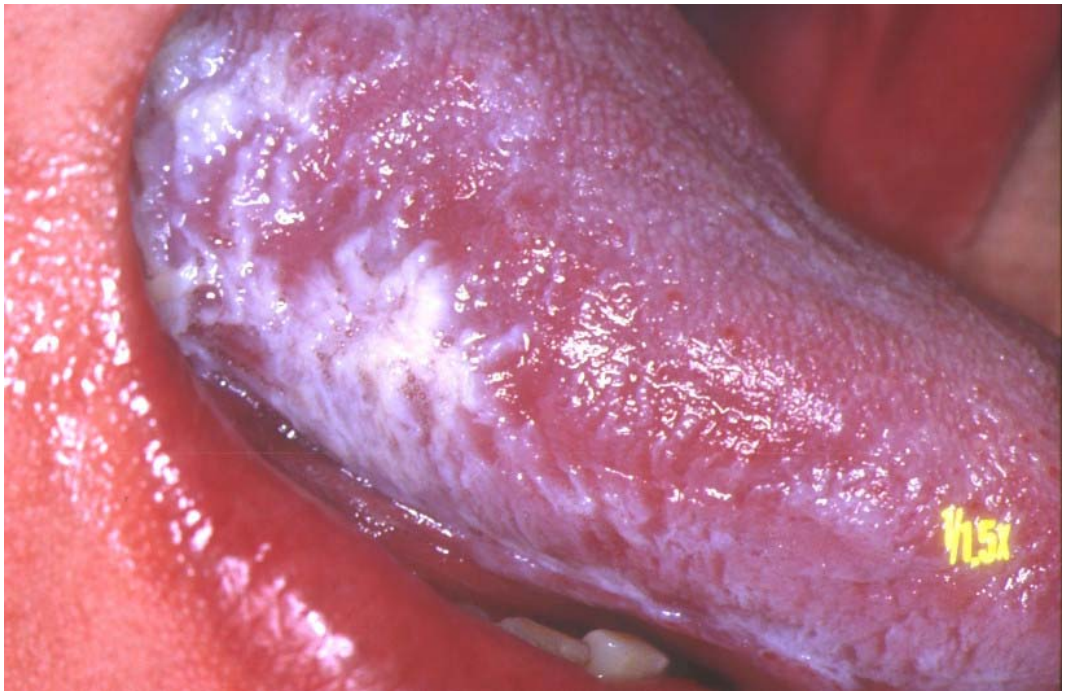

Figure 1. Hairy leukoplakia of the border of the tongue

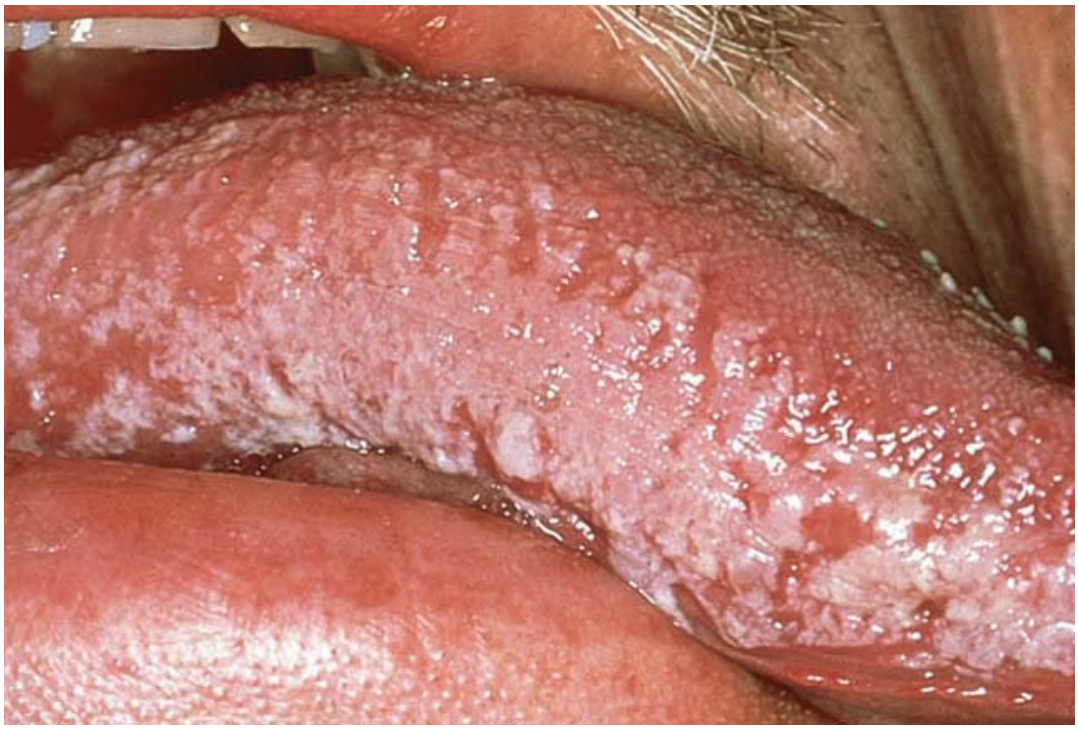

Figure 2. Hairy leukoplakia of the border of the tongue

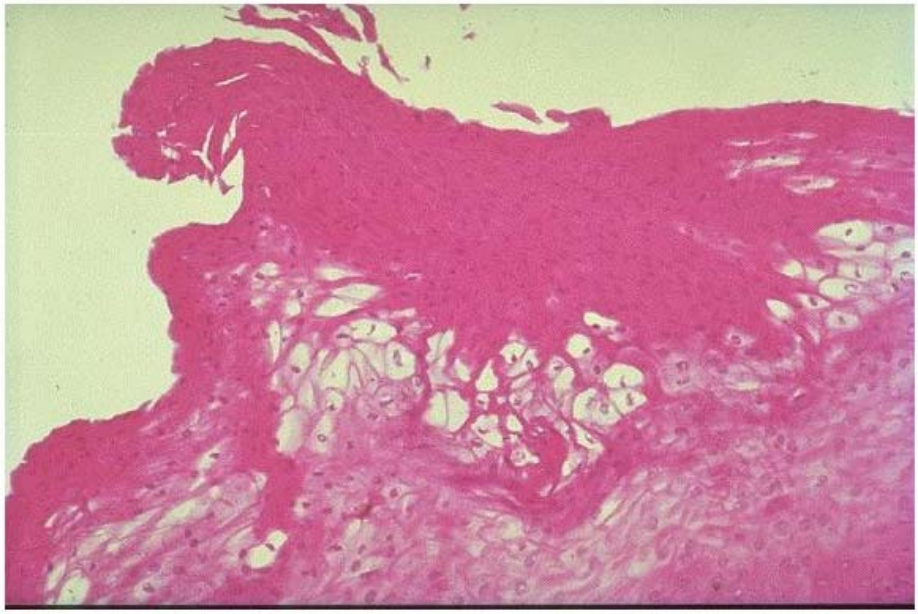

Figure 3. Hairy leukoplakia, histological aspect, showing hyperparakeratosis and pyknic cell nuclei (koilocytosis) indicating presence of virus (courtesy: prof JJ Pindborg, Copenhagen)

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HERPES SIMPLEX VIRUS (HSV) INFECTION OF THE MOUTH

Definition

Herpes viruses are a large family of parasites able to infect humans. All are DNA viruses capable of latency. Among human herperviruses there are two variants - Herpes Simplex Virus type-1 (HSV-1) and type–2 (HSV-2), which can be – as well as other clinical signs and symptoms – responsible for oro-facial disease. Usually HSV-1 infections affect the face and mouth while HSV-2 infections occur genitally. Both viruses may cause recurrent disease.

HSV usually enters humans via the mouth. Oro-genital and penetrative intercourse, contact sports, some high risk occupations and corneal transplant surgery have been associated with HSV transmission.

The first episode of HSV infection in humans who have not previously been exposed to HSV-1 and HSV-2 is called the *primary* infection. Symptoms are not always present during the first infection, and therefore patients may be unaware that they have been exposed to the virus. Following primary infection the virus travels through the nerves that give sensation to the area infected. Once it enters the root of these nerves – the ganglion – it remains there for life. When the virus reactivates, it can cause mucosal or skin lesions in roughly the same area to that where it originally entered the body: these manifestations are defined as *recurrences*.

Epidemiology

HSV-1 and HSV-2 occur worldwide and have no seasonal variation. HSV infection is rarely fatal. Most human beings have been infected and harbour latent virus that can reactivate; hence there is a vast HSV reservoir for transmission to susceptible individuals. Demographic factors affect acquisition of HSV-1 infection. In less developed countries seroconversion happens early in life – at 5 years in around a third of children and in 70-80% by adolescence. In comparison, individuals in more developed countries become infected later on – seroconversion occurs in about 20% of children younger than 5 years; then no substantial rise in frequency happens until an increase to 40-60% at age 20-40 years. In the USA, race also affects acquisition of HSV-1. By age 5 years, more than 35% of African-Amerindians versus 18% of white children are infected with HSV-1. Incidence of infection among university students is around 5-10% annually.

HSV-2 infections are usually sexually transmitted. Most genital HSV infections are caused by HSV-2; however an increasing proportion is attributable to HSV-1. Genital HSV-1 infections are usually less severe and less prone to recur than those caused by HSV-2. HSV-2 seroprevalence rises from about 20-30% at age 15-29 to 35-60% by age 60 years. Factors that affect acquisition of HSV-2 infection include sex (infection is more frequent in women), race (infection is more frequent in Africans Americans than whites), marital status, number of sexual partners, and place of residence (prevalence is higher in city than in suburbs).

As with HSV-1 infection of the mouth, HSV-2 primary, initial or recurrent infection can be symptomless. Recurrence varies between men and women, occurring 2.7 and 1.9 times per 100 days, respectively. Women with initial genital herpes can shed the infection without symptoms; this occurs in 12%, 18% and 23% of primary HSV-1, primary HSV-2 and non-primary-HSV-2 infections respectively.

Clinical presentation

Herpesvirus infections can cause debilitating diseases which, in persons with frequent recurrences, may have psychological and physical sequelae. *Gingivostomatitis and orolabial HSV infection* are expression of trigeminal nerve infection. Gingivostomatitis is a symptomatic primary HSV-1 infection, usually occurring in children and characterized by vesicles and ulcers in and around the oral cavity (Figure 1). Children are often unable to swallow because of the associated pain, and may become dehydrated. In severe cases hospitalization may be required and occasionally autoinoculation can result in conjunctivitis and keratitis. In cases of oral disease, primary infection is usually inside the mouth (gingivostomatitis), whereas recurrent disease is most commonly associated with lesions of the lip (herpes labialis or cold sores) (Figure 2) or cutaneous manifestation (facial herpes). Cold sores are usually preceded by prodromal symptoms as tingling, pain, burning sensation or itching at the site of reactivation. Symptomatic outbreaks of cold sores are estimated to affect 20-40% of adults. Occasionally reactivation may result in irregular oral ulceration in the distribution of the affected nerve (Figure 3).

Reactivation of HSV-1 from the geniculate ganglion has been implicated in the pathogenesis of idiopathic *facial palsy or Bell's palsy*.

Ocular HSV infection is a major cause of corneal scarring and visual loss which is the result of a direct viral cytopathic effect.

Aetiopathogenesis

Herpesviruses have two biologic properties: the ability to invade and replicate in the host nervous system and the ability to establish a site of latent infection. The neurovirulent properties of herpes simplex virus (HSV) enable the virus to cause a disease primarily of the sensory nervous system rather than of the skin. The ability of HSV to infect and cause lyses of cells of the central nervous system (CNS) is illustrated by sporadic cases of potentially fatal HSV encephalitis. In more usual circumstances, however, the main target of the virus is the peripheral nervous system. During primary infection, virus is transported via sensory ganglia to establish a chronic latent infection, most commonly in the trigeminal, cervical or lumbosacral ganglia. Retrograde transport of HSV along nerves and the establishment of latency are not dependent on viral replication in the skin or neurons therefore neurons can be infected in the absence of symptoms.

Periodically HSV may reactivate from its latent state and virus particles then travel along sensory neurons to the skin and other mucosal sites to cause recurrent disease episodes. Recurrent mucocutaneous shedding of HSV can be associated with lesions or asymptomatic shedding and in either scenario is allied with a period when virus can be transmitted to a new host.

Diagnosis

Although acute herpetic gingivostomatitis and recurrent labial and intraoral herpes simplex infection are diagnosed by the clinical history and signs several laboratory techniques may assist in the diagnosis of the difficult case. These include:

- Morphologic studies (Tzanck test) – smear taken from an intact vesicle
- Viral culture, antigen or DNA studies (Immunomorphologic, immunovirologic, molecular virologic methods)
- Serologic – a rising titre of serum antibodies is confirmatory, but gives the diagnosis retrospectively

Treatment

Primary stomatitis

An adequate fluid intake and soft diet must be encouraged. Dehydration especially in children may result in hospital admission. Antipyretic/analgesic agents such as paracetamol (acetoaminophen) relieve pain and fever (aspirin should be avoided in children). Local pain control may be assisted by the use of benzydamine hydrochloride 0.15% mouthwash/spray or lidocaine hydrochloride 1% gel. A 0.2% aqueous chlorhexidine mouthwash (diluted to half strength with warm water if too uncomfortable at full concentration) or tetracycline mouthwash (contents of 250mg capsule of tetracycline or doxycycline dissolved in 15ml warm water and held for 2-3 minutes and expectorated four times daily) may assist in resolution of painful ulceration by decreasing secondary bacterial infection.

Three randomised controlled trials (RCTs) have clearly demonstrated that early aciclovir treatment significantly shortens the duration of all clinical manifestations and infectivity of affected children compared with placebo. Treatment should be started within the first 3 days of disease onset. The proposed therapeutic dose is 15 mg/kg, 5 times daily for 5 to 7 days.

Recurrent herpes labialis

Prevention

Oral antiviral agents . Limited evidence from RCTs suggests that prophylactic oral antiviral agents may reduce the frequency and severity of attacks compared with placebo, but the optimal timing and duration of treatment is uncertain. Long term prophylaxis should be reserved for those subjects who suffer regular severe attacks.

Sunscreen Limited evidence from two small crossover RCTs suggest that ultraviolet sunscreen may reduce herpes recurrence compared with placebo.

Topical antiviral agents There are no RCTs on the effects of topical antiviral agents used as prophylaxis.

Treatment

Oral aciclovir for first attack One small RCT in children found that oral aciclovir reduced the mean duration of pain compared with placebo. Another small RCT in children found that oral aciclovir reduced the median time to healing compared with placebo.

Oral antiviral agents for recurrent attack Two RCTs found that oral aciclovir (if taken early in the attack) marginally reduced the duration of symptoms and pain compared with placebo. More recently valaciclovir has showed similar results.

Topical antiviral agents for recurrent attacks Limited evidence from RCTs suggests that topical 1% penciclovir or aciclovir reduced the duration of pain and symptoms compared with placebo.

Topical anaesthetic agents One small RCT found limited evidence that topical tetracaine reduced the mean time to scab loss compared with placebo. However, the clinical importance of this result is unclear.

Topical antiviral agents for first attack There are no RCTs on the effects of topical antiviral agents.

Zinc oxide cream One small RCT found limited evidence that zinc oxide cream reduced time to healing compared with placebo but found that it increased the risk of skin irritation.

Prognosis

Whilst antiviral agents prevent recurrence, it is most unlikely that HSV is eradicated and therefore, despite therapy, long-term reactivation may be expected.

Complications

Eczema herpeticum

HSV infection is a particularly troublesome complication of atopic eczema and frequently affects the head and neck if associated with autoinnoculation from oro-labial herpes. Eczema herpeticum is a potentially serious and progressive disease from which suppressive therapy with acyclovir is indicated.

Erythema multiforme and Stevens-Johnson syndrome

HSV is a recognised trigger for these mucocutaneous diseases: continuous aciclovir therapy (600mg twice daily for 6 months) can be effective in preventing outbreaks.

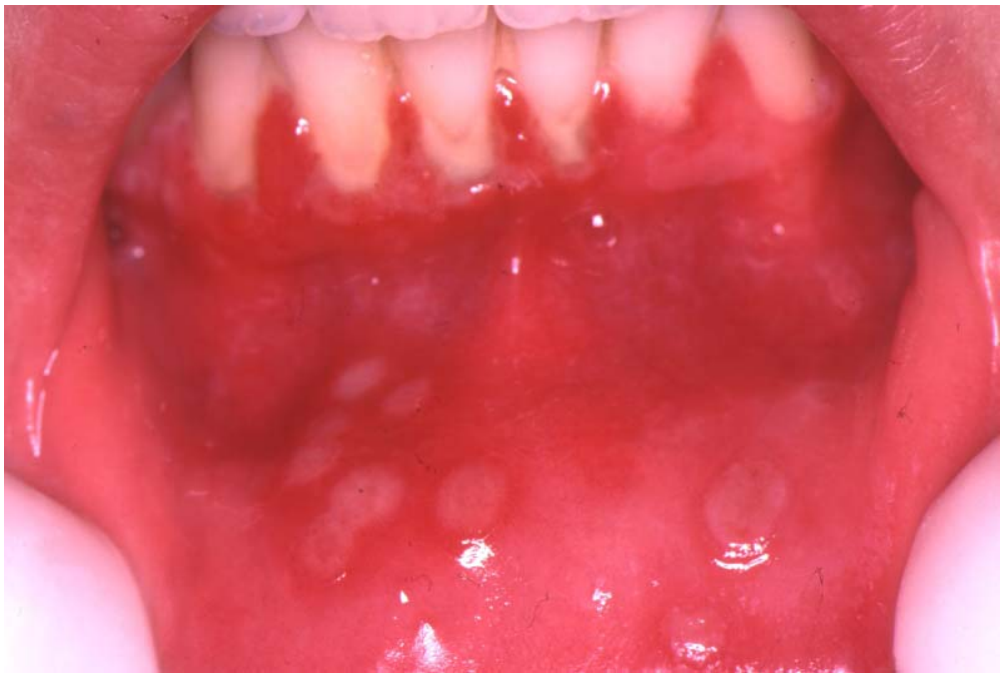

Figure 1 Herpes gingivostomatitis

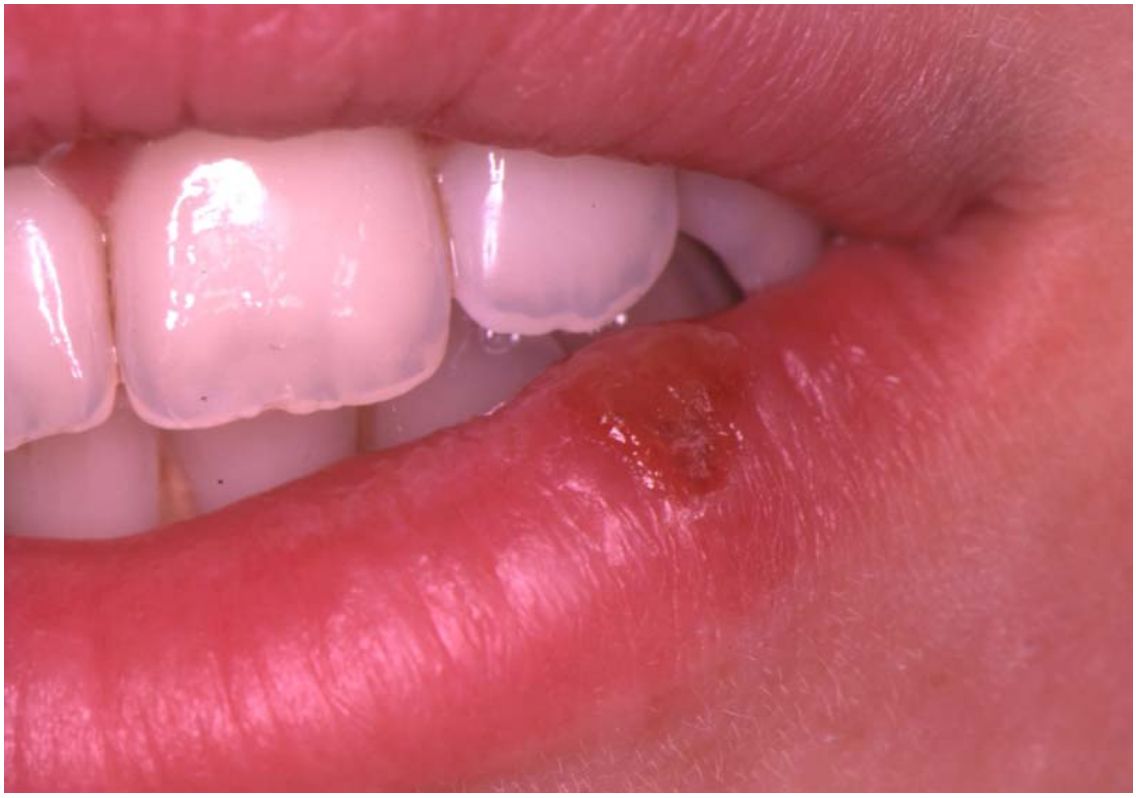

Figure 2. Herpes lesions of the lip (cold sore)

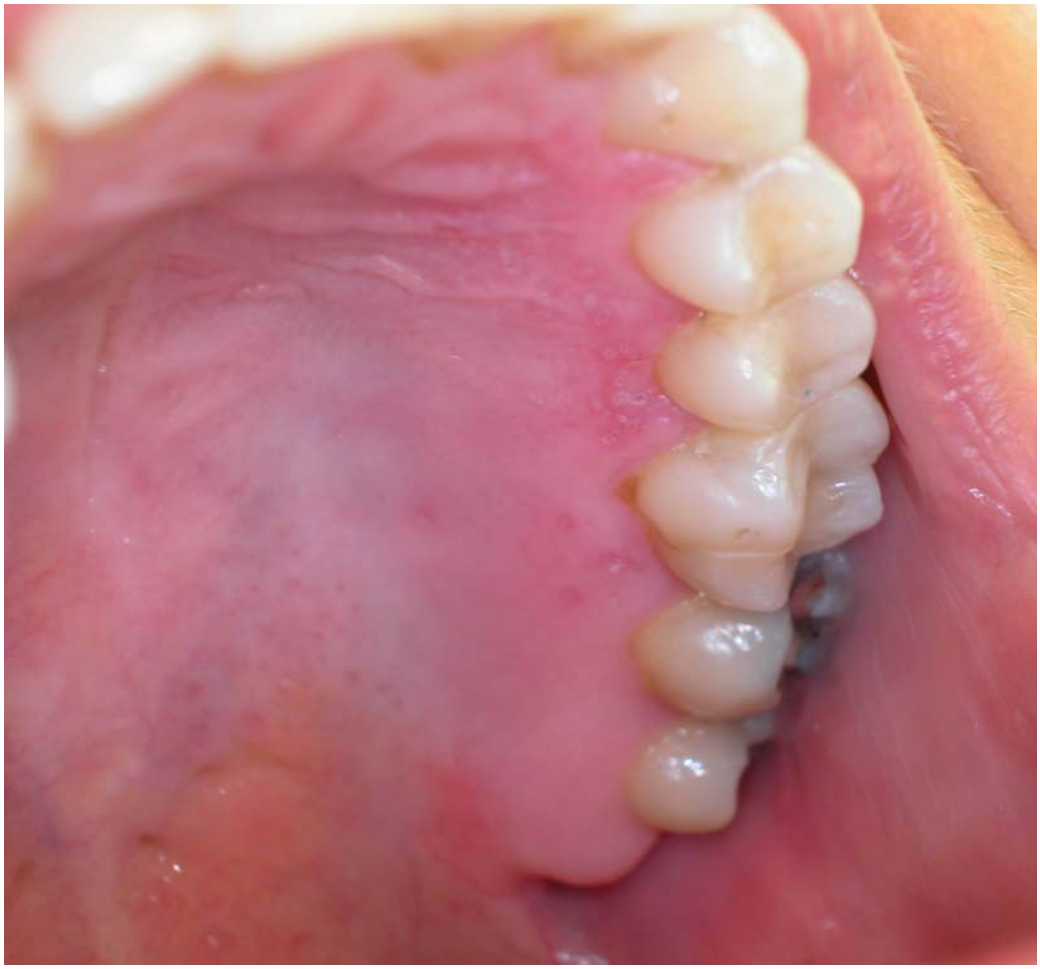

Figure 3. Herpes lesions of the palatal mucosa, recurrence.

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Links

http://www.ihmf.org/

http://www.ahmf.com.au

http://www.herpes-foundation.org/

HERPES ZOSTER INFECTION

Definition

Varicella-zoster virus (VZV), also known as Human Herpes Virus III (HHVIII), is a member of the herpes virus group. As all the other viruses from this group, VZV can manifests itself as a recurrent infection. After entering the body and causing primary infection, varicella-zoster virus remains latent in the neurons of sensory ganglion, especially dorsal roots of ganglion of the spinal nerves and extramedullar ganglion of the cranial nerves. Reactivation of the VZV infection is easily triggered by immune suppression. VZV infection is common in elder persons, immunocompromised or HIV positive individuals, and patients affected by malignant blood dyscrasias, malignant tumours, or undergoing immunosupressive therapy and radiotherapy.

Epidemiology

Varicella (chickenpox) is the primary infection of VZV and it is very common among children of both sexes. Herpes zoster (shingles) is the recurrent form of infection and occurs in the 3-5% of population, mainly among older individuals and immunocompromised. One percent of the persons who are 80 years old may have an infection during the period of one year. In 10% of HIV positive patients, HIV disease starts with herpes zoster infection in the oral cavity as an oral opportunistic infection. Reactivation of infection is infrequent in younger people and children. Postherpetic neuralgia, a significant pain or dysaesthesia present 3 or more months after herpes zoster, approximately 10–20% of zoster patients of all ages are affected, but frequency increases with age.

Clinical manifestations

Herpes zoster (HZ) in the oral cavity results from the involvement of second and third branch of the trigeminal nerve.

HZ develops 2-4 days after prodromal period, manifesting itself with general symptoms, such as fever, weakness, fatigue, and neck stiffness. Paresthesia and burning sensation in the region of the affected nerve are also frequent consequences of the VZV infection. Characteristic sign of oral HZ is the presence of unilateral vesicles that break rapidly, leaving small ulcers. On skin and lips, vesicle rupture can result in erosions covered by pseudomembranes and haemorrhagic crusts. Oral lesions without facial skin involvement are rather infrequent. Crusts and pseudomembranes, developing during the first week of vesicle formation, usually disappear in the second or third week. The patient is contagious from 48 hours

before vesicle formation, until oral lesions heal. It is possible that HZ occurs without lesions ("herpes sine herpete" zoster without eruptions), when only neurological symptoms are present. A frequent complication of HZ infection is postherpetic neuralgia (PHN). PHN, which is not correlated with immune suppression, is characterised by pain, paresthesia, hyposthesia or alodynia and can persist for months and year. Neuralgic pain is frequently associated with sensory loss.

Etiopathogenesis

Following primary infection, the virus is latent in the neurons of the sensory ganglia and reactivates itself as a consequence of immunodefficiency. The inflammation of the ganglion is followed by hemorrhagic necrosis of the nerves together with a partial necrosis of the ganglion. VZV affects neighbouring neurone ganglia and it might affect several branches of the nerve. Viruses spreading through sensory parts of the second and third branch of the trigeminal nerve, lead to the pathological changes in the oral cavity. The viral presence further leads to the acantholysis in the prickle cell of the epithelium and formation of the vesicles. Because of the subtle overlying layer, vesicles rupture rapidly, leaving erosions. VZV damages peripheral nerves through demineralisation, leading to sclerosis and degeneration.

Diagnosis

Diagnosis is made on the basis of clinical manifestations and subjective symptoms, presence of the viral antigens as well as presence of antibodies against VZV. Differential diagnosis of other viral infections is also possible so this infection must be well documented. The best laboratory diagnostics are PCR and direct VZV identification in the cell culture of human fibroblasts. The sample should be taken from vesicle or serum. The presence of VZV is evidenced by direct immunofluorescence of antibodies against VZV from the vesicle and up to 80% of the VZV infections could be detected using this method. Serological findings are helpful in recurrent VZV infections and show increased IgM, ten days after eruptions and increased IgG and IgA four days after the eruptions. Serological tests which reveal antibody titers might be useful in immunocompromised patients.

Treatment

Therapeutic regimens have become more efficient nowadays, especially when they are applied 48-72 hours after the appearance of the oral lesions. Systemic intake of antiviral agents is urgent in the patients who are older than 50 years of age, in immunocompromised, and in all patients with infection of the head and neck region,

especially in those with HZ of the ophthalmic branch. In adult immunocompetent subject of less than 50 years of age, symptomatic treatment is generally sufficient. Acyclovir, valacyclovir, famciclovir or brivudin must be administered systemically. Valacyclovir is proven to be more efficient when compared to the acyclovir. Brivudin showed higher antiviral potential then acyclovir, valacyclovir and famciclovir. Brivudin is also more easily administered (i.e. once a day during 7 days) and has no nephrotoxic properties.

Systemic use of the antiviral drugs shortens the healing period and lessens the pain symptoms together with prevention of other acute and/or chronic complications. Treatment of PHN usually comprises of analgesics together with neuroactive agents as well as with antiviral drugs. Corticosteroids administered systemically during the first two weeks of the disease are helpful in the PHN prevention, but they should not be given when PHN is already present. Some authors suggested combination of the perilesional anesthetic and corticosteroid injections. Reports upon shortening of the period of healing, but not PHN prevention have been documented. While treating neuralgia, analgesics, neuroactive agents and B vitamin complex should be administered. Some trials suggested that tryciclic antidepressants can be effective in alleviating neuropatic pain.

Prognosis and complications

Complications can occur in 10-46% patients with herpes zoster infection. Severe immunodeficiencies which precede HZ infection might predispose viral dissemination in the visceral organs, microbial superinfection and staphylococcal sepsis. Disseminated HZ infection might manifest as pneumonia, meningitis, encephalitis and hepatitis, as well as dermatological diseases. Paresis of facial nerve might develop as a complication when ganglion oticum is affected. When HZ affects the first branch of the trigeminal nerve, serious damage of the eye might occur (zoster ophtalmicus). Oral consequences of HZ might include heavy scarring, pulpal necrosis and internal root resorption. Also, cases of bone necrosis with teeth loss in immunocompromised patients with long term HZ have been described. Finally, patients suffering from recurrent HZ may have increased incidence of malignant diseases.

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Links

www.ihmf.org/default.asp International Herpes Management Forum (accessed on 1 July 2004).

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HPV INFECTION AND RELATED ORAL DISEASES

Definition

Human Papillomaviruses (HPVs) are a group of DNA viruses, which have a remarkable target cell specificity: they have been reported principally in anogenital tract, urethra, skin, larynx, tracheobronchial mucosa and oral cavity. More than 100 different types of HPV have been classified and they are divided into high (e.g. 16,18, 31) and low oncogenic risk genotypes (e.g. 11, 42, 36), depending on the association with malignant change. The viral products stimulate cell growth in the basal layer leading to formation of a common wart. Since the recognition of high risk HPVs in oral carcinomas, the malignant potential of HPV infection has been suggested. A recent metanalysis, including 94 studies about HPV presence in oral mucosa (range 0-100%) showed that oral dysplasia and oral squamous carcinoma are more commonly associated with HPV infection (type 16 and 18) compared with normal oral mucosa.

Epidemiology

As regards healthy oral mucosa, the prevalence of HPV has been reported to vary greatly, ranging from 0% to 81.1%; recent datum is 0.6% for Japan and 5.5 % for Italy.

Clinical presentation

HPV can be found in oral lesions of different clinical appearances and significance, ranging from benign warts to malignant neoplasms. Immune status and genetic profile of the host as well as the type of virus, may play a role in determining the clinical outcome of HPV infection.

The most common among these entities is a benign, focal, exophytic lesion usually designated with the general term of *oral papilloma*, although many terms can be used to indicate the clinical variants of such lesion; among them being *oral verruca vulgaris*, *oral condyloma acuminatum*, *oral focal epithelial hyperplasia*. It has been suggested that the clinical presentation of oral papillomas depends from the type of HPV that is present in the lesion, although no definitive evidence is available in this regard. Generally oral papillomas are asymptomatic, unless they are traumatized and interfere with mastication.

HPV has been detected in several other oral lesions, including malignant and premalignant lesions such as squamous cell carcinoma, leukoplakia (especially in the proliferative verrucous entity - PVL) and lichen planus. HPV-DNA from different types can be found also in clinical healthy oral mucosa, where is usually present in its latent form (episome).

Etiopathogenesis

HPVs are epitheliotropic and host-specific, with infection across the species being exceedingly uncommon. Historically, it has been postulated that HPV infection begins with the inoculation of virus into interruption of epithelium and the interaction with a putative specific cellular receptor. It is recognized that HPV, following trauma of epithelium, establishes a non-productive infection of basal layer cells in the skin and mucosa, but it is only in differentiated epithelia that HPV replicates. The early viral gene products stimulate cell growth in the basal layer, leading to epithelial proliferation and formation of an exophytic lesion, consisting of thickened layers of epithelial tissue that may show acanthosis or hyperkeratosis, in presence of an intact basement membrane. *In vitro* studies have suggested that HPV may act as an initiator of epithelial proliferation or play a role in the early stage of oral carcinogenesis through mechanisms involving E5, E6, and E7 oncoproteins which can degrade oncosuppressor gene products p53 and pRb.

Route of transmission

HPVs can be sexually transmitted (via multiple sexual partners, unknown partners, oro-genital contact), although alternative routes have been demonstrated, among them vertical (perinatal) or horizontal transmission (HPV-contaminated fomites and clothing). Autoinoculation of the virus is common.

The incubation period for HPV ranges from 1-6 months; however, latency periods of up 3 years or more are suspected.

Diagnosis

The diagnosis of HPV-associated oral lesions is essentially clinical, but histological confirmation is normally recommended. Although identification of specific HPV type has no clinical relevance at present, exfoliated cells can be easily collected by brushing procedure and HPV-DNA amplified by *nested* PCR assay.

A variety of molecular methods exist for detection and quantification of HPV but there are essentially three techniques using nucleic acid probes (Direct Probe Methods, Signal Amplification, Target Amplification).

Treatment and prognosis

The first line treatment for oral papilloma is surgical excision with scalpel, although alternative approaches include cryosurgery with liquid nitrogen, or electro-cauterization. There is currently no virus-specific drug therapy available for HPV infection. Local medical treatments include topical application of trichloroacetic acid, podophyllum,

cidofovir, imiquimod, and intralesional injection of antiviral agents. Among systemic therapies, ribavirin, retinoids, folic acid, interferon and others have been evaluated without significant success.

A follow-up examination should be done by the health care provider every few weeks after initial treatment, then self examination can be promoted in order to detect reccurrences. Current treatments of HPV-associated lesions may reduce, but unfortunately, do not eliminate their infectivity.

Treatment can be difficult, with frequent failures and recurrences, even if some lesions may resolve spontaneously.

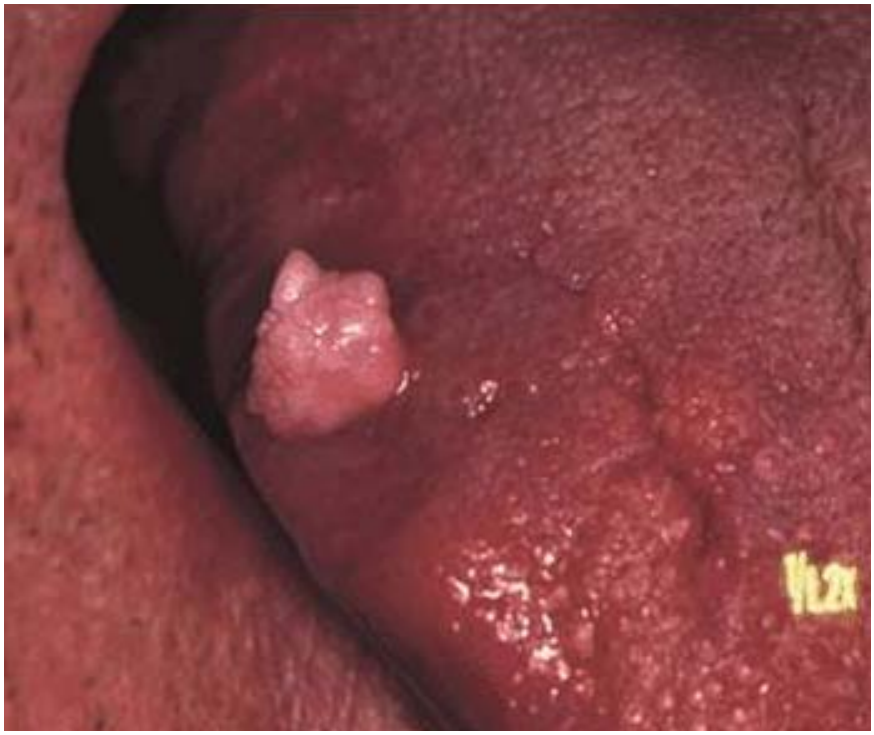

Figure 1. HPV associated lesion of the tongue

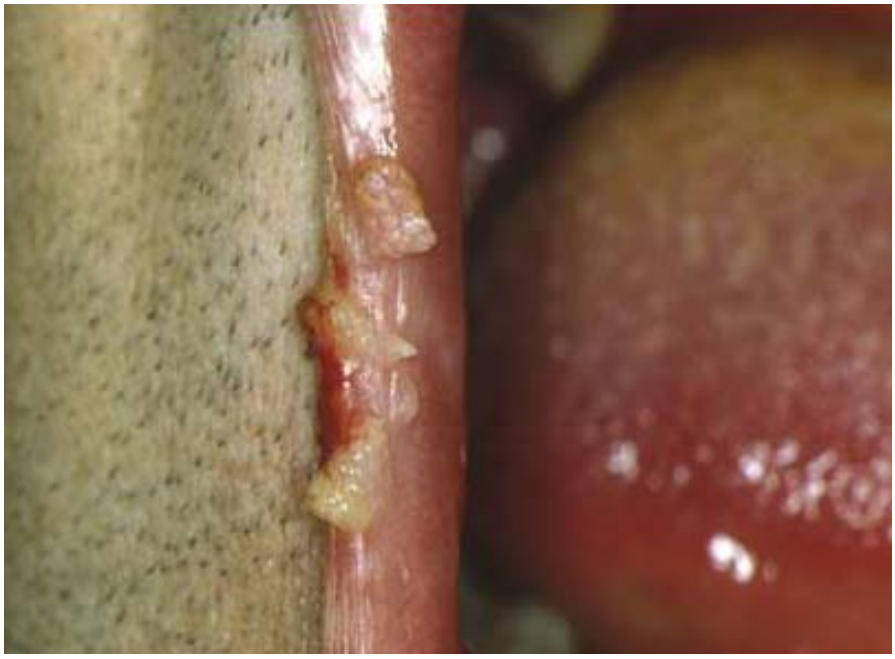

Figure 2. HPV associated lesion of the commissure

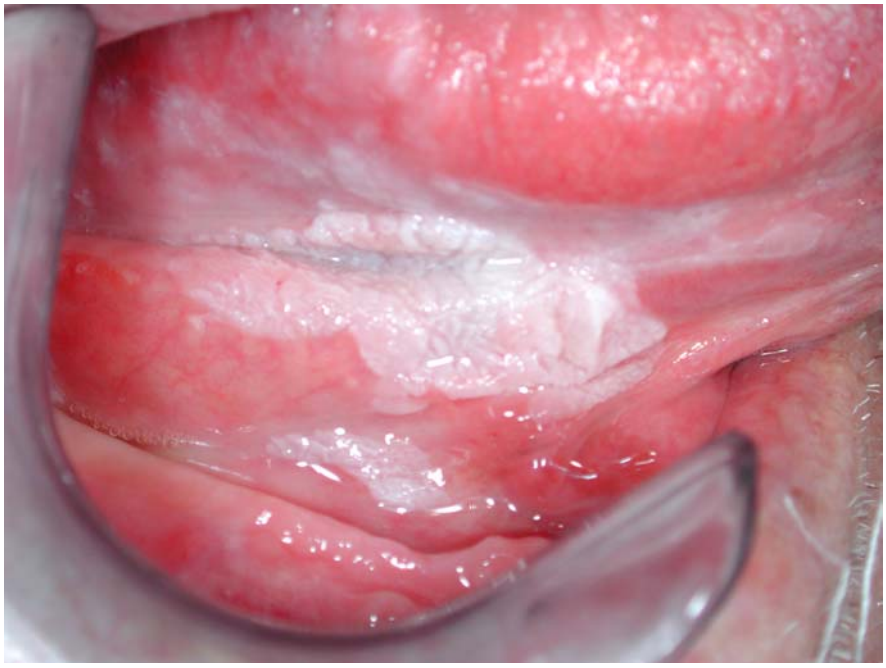

Figure 3. HPV associated leukoplakia

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IATROGENIC XEROSTOMIA

Definition and terminology

Xerostomia means dry mouth (Greek ξερος: dry, στομα: mouth). Traditionally, the term has been used to describe both the subjective feeling of dry mouth, i.e. the patient's own conception of dry mouth, as well as the objectively assessed signs suggesting dry mouth (Table 1). More recently, it has been suggested that ”xerostomia” should be used in its first-mentioned connection as a subjective feeling of the patient, while expressions such as ”reduced salivary flow” and ”hyposalivation” should be used when discussing the objective condition of the patient by whom salivary flow rate has been measured and found to be reduced or even extinct. This terminological issue is further complicated by the fact that not all patients with objectively measured reduced salivary flow (hyposalivation) suffer from xerostomia and, vice versa, many patients who report subjective feeling of dry mouth (xerostomia) show salivary flow rates not meeting the criteria for hyposalivation. This is because not only the amount of saliva is responsible for adequate wetting of the oral surfaces, but also the quality of saliva is important.

Epidemiology

There are now population studies on the prevalence of xerostomia or reduced salivary flow. However, among elderly people, xerostomia has been reported in more than 50% of the subjects and 10 – 25% of the elderly experience it constantly. Patients who underwent cancer treatment and received radiotherapy to the head and neck region, where salivary glands are subjected to primary radiation, often suffer severe and irreversible xerostomia due to damage to the secretory tissue. It has been shown that the mean radiation dose received by a salivary gland is correlated with the reduction of salivary flow. The range of mean cumulative doses to cause irreversible functional reduction of the salivary glands included in the radiation portal, is from 26 to 39 Gy. In most conventional schedules both tumour and normal tissues (i.e. healthy tissues surrounding the tumour that are included in the radiation portal) receive a cumulative dose exceeding 40 Gy. Newer radiation techniques (three-dimensional conformal radiation therapy) are designed to shape the spatial distribution of the high radiation dose to the target area, thereby reducing the dose delivered to the normal tissues, including salivary gland tissue.
Other subjects that can be affected by dry mouth include patients with autoimmune diseases (in particular Sjögren's disease, in its secondary presentation often combined with rheumatic diseases), individual taking drugs (Table 2) and post-

menopausal women. In general, complaints of dry mouth are more common among women than men. In irradiated patients, xerostomia has a sudden onset, while in auto-immune diseases there is a more gradual development of a dryness sensation. In post-menopausal women, as well in patients suffering from drug-induced xerostomia, oral dryness usually is of a lesser extent as salivary secretion can often still be stimulated.

Clinical presentation

In addition to dry mouth with its characteristic consequences to the teeth and mouth mucosa as given in Table 1, reduced salivary flow may be associated with a variety of other symptoms. These are presented in Table 3.

Etiopathogenesis

Saliva is secreted from the salivary glands. There are three pairs of major glands and hundreds of minor glands. The major glands are: *the parotid glands*, situating in front and underneath the ear lobes, which duct ends in the buccal mucosa adjacent to upper molar teeth; *the submandibular glands* and *the sublingual glands*, both situating in the bottom of the mouth and delivery saliva through a common duct ending on the side of the tongue fraenulum, thus wetting the floor of the mouth. The major glands are responsible of the watery saliva flowing into the oral cavity when secretion is stimulated. In particular, parotid gland saliva is watery (serous) and contains high concentrations of amylase, a digestive enzyme causing starch to turn to glucose and fructose. Submandibular and sublingual saliva is ”mixed” with both serous and viscous (sticky) secretions. Mucins (a very large protein molecule with many sugar side chains) are responsible for the viscous behaviour of submandibular and sublingual secretions, a characteristic that is important for the well-being of the mucosa (moistening and protective function).

The minor salivary glands are situated in the oral mucosae over nearly all the mouth. They are particularly numerous in the palate and inner aspects of the lips. Their secretion is viscous and the function is to lubricate the mucous membranes. The secretion of the minor glands is active all the time, while the activity of the other glands follows a diurnal rhythm, so that the production of saliva is lowest during night and highest in the afternoon. The secretion of the parotid glands is reduced to zero during sleep, while the secretions of the submandibular and sublingual glands reduce to a basal level.

Salivary output and flow rate values are highly individual. Salivary secretion is a complicated process regulated by the autonomic nervous system, so that both the

parasympathetic and sympathetic nerves stimulate the secretory units of the salivary glands. The nervous regulation is affected by the psychic state and alertness of the patient. Stress and tension cause a sensation of a dry mouth, while salivation is increased by merely thinking of something delicious or sour, such as imagining the sucking of a lemon.

The general body fluid balance is of key importance for salivary secretion because the watery saliva in particular is dependent on osmotic pressure of body fluid. Thus, dehydrated patients have less saliva.

There are hundreds of drugs that interfere with salivary secretion, mostly inhibiting salivary output. Examples of such drug categories are given in Table 2. Basically the more drugs a patient uses daily, the more prone he/she is for xerostomia and reduced salivary flow (Fig. 1).

Diagnosis

Salivary flow rates of whole saliva (pooled saliva that can be collected by e.g. a drooling or spitting method) and glandular saliva (separate collection of secretions of the parotid and submandibular/sublingual glands) can be obtained without stimulation (resting saliva) and after mechanical (chewing) or gustatory (e.g. citric acid) stimulation. In this way, it can be easily deduced whether sufficient saliva is secreted under resting conditions. In addition, assessment of salivary gland function shows to what extent stimulation of the salivary flow is possible, which salivary glands still can be stimulated to a significant flow, and in which cases supportive oral care (stimulation therapy) might be successful. When successful stimulation of saliva flow is not possible, only palliative oral care can be provided.

The assessment of resting flow needs collection of saliva under peaceful, quiet circumstances with as few outer stimuli as possible. It is commonly measured by having the patient seated undisturbed and asking him/her to let all saliva coming in the mouth to flow into a receptacle without any chewing movements. The collection time should be long enough for a reliable reading; from 5 to 15 minutes depending on the patient's secretory capacity. A commonly applied clinical reference limit for reduced resting whole salivary flow rate is 0.1 ml/min when the free flowing method is used for measuring. Values below this threshold indicate reduced flow rate or hyposalivation.

Stimulated whole salivary flow can be measured with several means of stimulation. Citric acid drops on the tongue surface cause saliva to flow, as does chewing. Standard piece of paraffin wax (2 g) is a commonly used method for assessment of stimulated salivary flow rate. Here the patient is again seated undisturbed and given

the paraffin wax to chew at a constant rate of approximately once a second. Saliva secreted during the first 30 seconds is discarded (to remove debris and food remnants), and collection into a receptacle is then started and continued for usually 5 minutes so that the patient spits all saliva into the receptacle. The clinical reference limit for paraffin-wax stimulated whole salivary flow rate is 0.7 ml/min. Thus, values below this threshold indicate hyposalivation or reduced flow rate.

Treatment

Drinking enough fluid daily is of key importance to a patient with dry mouth. The amount of recommended daily fluid intake of an adult is 1.5 - 2 L. Elderly patients seldom drink that much, and the clinician may therefore need to remind the patient to drink enough throughout the day. Because the patient's medication is often the cause of hyposalivation, the drugs should be checked, together with the physician in charge, in order to assess if an alternative, less xerostomic, drug or drug combination can be prescribed. Unfortunately this is seldom possible. Therefore, local remedies to relieve xerostomia and oral dryness need to be considered. Table 4 gives examples of preparations used to relieve xerostomia.

Medical therapy for hyposalivation is rarely considered a first approach, as many patients find relief by gustatory or mechanical stimulation of the salivary glands. Cholinergic drugs such as pilocarpine tablets (5 mg two to four times daily) are available in many countries and they suit patients with no contraindications for using such preparations. These include irradiated patients who are otherwise healthy and some patients with Sjögren's syndrome. Also the use of cevimeline has been advocated (with probably less side effects than pilocarpine), but this drug is not available yet in Europe. Acupuncture has been reported as resulting in some relief of the dryness related complaints.

When the function of the salivary glands is nearly completely destroyed, stimulatory measures can have no effects. In these cases some palliation can be obtained by wetting the oral tissues with home-made or commercially available products, including special tooth pastes, oral gels, mouthrinses and saliva substitutes (Table 4). Not all patients rate the effectiveness of saliva substitutes higher than that of moistening the mouth with water, although it is known that water is a very poor agent for prolonged moistening of the oral mucosa, as short after moistening the oral mucosa feels dry again. Therefore it is worthwhile to assess the effect of various saliva substitutes in each individual patient.

As a guide for the palliative treatment of hyposalivation the following recommendations can be used:

- *Severe hyposalivation*: A saliva substitute with gel-like properties should be used during the night and when daily activities are at a low level. During the day, a saliva substitute with properties resembling the viscoelasticity of natural saliva, such as substitutes containing xanthan gum and mucin (particularly bovine submandibular mucin) should be applied.
- *Moderate hyposalivation*: If gustatory or pharmacological stimulation of the residual salivary secretion does not provide sufficient amelioration, saliva substitutes with a rather low viscoelasticity, such as substitutes which have carboxymethylcellulose, hydroxypropylmethylcellulose, mucin (porcine gastric mucin), or low concentrations of xanthan gum as a base are indicated. During the night or other periods of severe oral dryness, the application of a gel is helpful.
- *Slight hyposalivation*: Gustatory or pharmacological stimulation of the residual secretion is the treatment of choice. Little amelioration is to be expected from the use of saliva substitutes.

Prognosis and complication

Unfortunately, dry mouth and xerostomia are chronic conditions with little prospect of permanent resolution. Therefore, it is important that the patient understands the condition and learns to cope with it. Only in select cases xerostomia may subside. These include menopausal women whose reduced saliva flow may increase after the new hormonal balance when the climacteric is over. Some women with severe xerostomic symptoms benefit from hormone replacement therapy, but not all. Similarly, hyposalivation caused by irradiation may slowly subside provided that the tumour dose has not been targeted directly onto the salivary glands and the cumulative dose to the salivary glands does not exceed the critical limit of radiation injury to cause irreversible damage. As stated earlier, if the reduced salivary flow is a side effect of necessary medication, this can be changed. The patient's physician needs to be consulted whether alternative drugs with less mouth-drying effect might be available and suitable to the patient. The complications of reduced salivary flow are listed in Tables 1 & 3. Because the oral cavity is an important source of infection and saliva is one of the key defensive factors in the mouth, the lack of saliva may reflect in rampant caries or mucosal infections.

Prevention

Due to the aetiology of xerostomia and hyposalivation these conditions can seldom be prevented. All the remedies given in Table 4 must therefore be provided to the

patient in order to keep the teeth and mouth mucosa healthy. In addition, xerostomia patients with hyposalivation need frequent dental check-ups so that the dental diseases are controlled. Because these patients are also liable to dental erosion, acid beverages and acidic foodstuffs should be avoided. Daily oral hygiene should be taken care meticulously. In dentate patients frequent applications of neutral fluoride preparations are advocated.

Table 1. Symptoms and signs of dry mouth

• Saliva is viscous and foamy • Lips are cracked and fissured • Tongue is dry, burning and painful, may be lobulated or fissured • Cheeks are dry and may look pale • Mouth mucosa in general appears thin and has lost its glistening, mouth mirror and tongue blade attach easily at examination • Swelling of salivary glands • ”Milking” saliva from the glands produces only minor amounts of it • Taste disturbances	• Excessive dental caries, caries lesions often located at sites which normally do not show signs of decay, such as approximal surfaces of lower anterior teeth, tooth cusps, and cervical regions of the teeth • Dental erosion (chemical wear) and cracking of tooth enamel, amongst others related to the combined effect of a lower pH and buffer capacity of saliva • Retention of food remnants in the mouth and dentition due to decreased clearance by saliva flow. Food remnants often can be observed for hours to more than a day after a meal. • Candidiasis (may appear as red or white lesion or removable plaque, or as cheilosis)

Modified from Sreebny 1996, Närhi et al. 1999 and Vissink et al. 2003.

Table 2. Examples of medications that may cause xerostomia

• Anticholinergic agents e.g. scopolamine, biperidine, atropine • Medications with anticholinergic effects e.g. disopyramide, clonidine, metoprolol, amitriptyline, levomepromazine, melperone, selegiline • Psychotropic agents e.g. diazepam, tsopiclone	• Medications causing changes in fluid and electrolyte homeostasis e.g. cyclothiazide, furosemide • Antineoplastic agents e.g. methotrexate, cyclophosphamide • Others e.g. bromhexine

Table 3. Non-oral symptoms often associated with dry mouth

• ”Thirst”, i.e. an increased need to moisten the oral mucosa • Difficulty with eating and swallowing • Difficulty with speech • Dryness of throat • Persistent cough • Dryness of nose • Dryness of eyes	• Nocturnal oral discomfort as the patients often awake because of their oral dryness • Dryness of skin • Constipation • Dryness of urogenital mucosa such as vagina • General symptoms: weakness, fatigue, joint pain, swelling and stiffness, generalized aching, weight loss, depression

Modified from Sreebny 1996, Närhi et al. 1999 and Vissink et al. 2003.

Table 4. Remedies and preparations for relieving xerostomia.

• Frequent fluid intake • Sugarless chewing gum • Sugarless lozenges and hard candies • Acid tasting substances (e.g. vitamin C tablet, lemon pastilles, be careful in dentate patients) • Saliva substitutes (special preparations sold over-the-counter in a pharmacy. Best effects have been reported by the xanthan gum or mucin containing ones)	• Olive or peppermint oil (recommended as small amounts to be taken into the mouth several times daily) • Avoidance of irritating food stuffs or oral hygiene preparations • Pharmacological stimulation (e.g. pilocarpine, cevimeline, carbachol, anetholetrithione)

Modifed from Närhi et al. 1999, Nieuw Amerongen and Veerman, 2003, Guggenheim and Moore 2003 and Vissink et al. 2003.

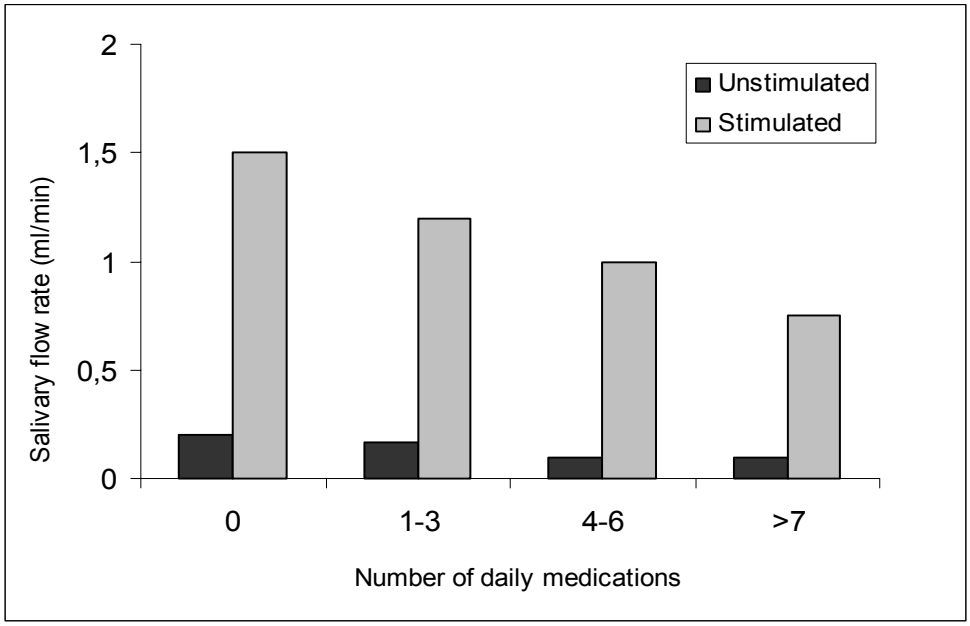

Figure 1. The more the patient needs to take concomitant drugs daily the less saliva is secreted. The black bars show the effect of increasing number of drugs daily on unstimulated salivary flow, the grey bars represent stimulated salivary flow (after chewing paraffin-wax). (Modified graph from Närhi et al. 1999)

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LEUKOPLAKIA

Definition

Leukoplakia is the most common premalignant or "potentially malignant" lesion of the oral mucosa.
Leukoplakia is a predominantly white lesion of the oral mucosa than cannot be clinicopathologically characterized as any other definable lesion.
The term leukoplakia is a clinical descriptor only and should not be used once histological information is available. On the other hand, the terms keratosis and dyskeratosis are histological features and should not be used as clinical terms.
Based on clinical examinations a provisional diagnosis of leukoplakia is made when the lesion cannot be clearly diagnosed as any other disease of the oral mucosa with a white appearance. A definitive diagnosis is made as a result of the identification, and if possible elimination, of suspected etiological factors and, in the case of persistent lesions, histopathological examination confirm the diagnosis.

Epidemiology

The incidence and prevalence of leukoplakia vary in different parts of the world.
In general the reported prevalence ranges from 0.2 to 5%, with remarkable regional differences: India (0.2-4.9%), Sweden (3.6%), Germany (1.6%), Holland (1.4%).
Leukoplakia is seen most frequently in middle-aged and older men.
Gender distribution is also variable. Men are more affected in some countries, while this is not the case in the Western world.

Clinical presentation

Leukoplakia can be either solitary or multiple.
Leukoplakia may appear on any site of the oral cavity, the most common sites being: buccal mucosa, alveolar mucosa, floor of the mouth, tongue, lips and palate.
Classically two clinical types of leukoplakia are recognised: homogeneous and non-homogeneous, which can co-exist.

- Homogeneous leukoplakia is defined as a predominantly white lesion of uniform flat and thin appearance that may exhibit shallow cracks and that has a smooth, wrinkled or corrugated surface with a consistent texture throughout. This type is usually asymptomatic.
- Non-homogeneous leukoplakia has been defined as a predominant white or white-and-red lesion ("eritroleukoplakia") that may be either irregularly flat, nodular ("speckled leukoplakia) or exophytic ("exophytic or verrucous

leukoplakia"). These types of leukoplakia are often associated with mild complaints of localised pain or discomfort.

Proliferative verrucous leukoplakia is an aggressive type of leukoplakia that almost invariably develops into malignancy. This type is characterised by widespread and multifocal appearance, often in patients without known risk factors.

In general, non-homogeneous leukoplakia has a higher malignant transformation risk, but oral carcinoma may develop from any leukoplakia.

Aetiopathogenesis

The aetiology of leukoplakia is still unclear. Although, tobacco seems to be the major inductor factor, its association cannot be determined in all cases.

A variety of smokeless tobacco habits have been reported as leukoplakia inductors: e.g. snuff, chewing. These lesions have shown to have a low malignant transformation risk.

A higher malignant transformation rate has been reported in *Candida*-infected leukoplakias. However, there is not an agreement of how this lesion should be named "*Candida*-leukoplakia" or "hyperplastic candidosis", and whether *Candida* infection is the cause of leukoplakia or is an infection superimposed in a pre-existing lesion.

The possible implication of human papillomavirus (HPV) and others virus has been studied. High risk HPV (16 and 18) have been associated with oral cancer.

Other factors such as alcohol, inadequate diet, vitamin deficiency (e.g. vitamin A and C), areca nut (betel), different mouthwashes, chronic traumatic irritation, poor oral hygiene, poor socio-economic status, galvanism, and even genetic factors have considered and studied in leukoplakia.

Diagnosis

Leukoplakia diagnosis has clinical and histopathological approaches.

- Provisional Clinical Diagnosis: clinical evidence from a single visit, using inspection and palpation as the only diagnostic means.
- Definitive Clinical Diagnosis: clinical evidence obtained by lack of changes after eliminating suspected etiologic factors during a follow-up period of 2-4 weeks (In some cases the time may be longer).
- Histopathologically Proven Diagnosis: definitive clinical diagnosis complemented by biopsy in which, histopathologically, no other definable lesion is observed.

Differential diagnosis includes lichen planus, lupus, leukoedema, candidosis, white sponge naevus, frictional lesions, *morsicatio* lesions, contact lesions, and smoker's palate.

Histopathological study of leukoplakia allows the clinician: 1.- to exclude any other definable lesions; and 2.- to establish the degree of epithelial dysplasia, if present.
It may be hazardous to just observe a white lesion without having taken a biopsy. It is important to biopsy the clinically most suspicious areas, especially the non-homogeneous zones or any associated red areas.
Other diagnostic methods such toluidine blue staining or Lugol's iodine, mycological culture and cytology might be helpful, but they do not replace the biopsy.

Treatment

There are different treatments for leukoplakia, which have shown different results. However, the risk of malignant transformation is not completely eliminated by any of the current therapies.
Initial treatment of a white oral lesion is the elimination of the possible aetiological factors: e.g. trauma, *Candida*, tobacco use etc. Complete and definitive cessation of tobacco is obligatory in patients with leukoplakia.
Presence of epithelial dysplasia in persistent lesions is a crucial aspect to consider, although measurement of DNA ploidy may be more reliable.
Complete surgical removal (leaving free-lesion borders) is recommended in cases with epithelial dysplasia. In cases without epithelial dysplasia the decision concerning further treatment or not, is influenced by the extent and location of the lesion as well as the patient 's medical condition.
Apart from surgical excision, other treatment modalities available include cryosurgery, laser surgery, retinoids, beta-carotene, bleomycin, calcipotriol, photodynamic therapy, etc.
The major drawbacks for most current agents are the frequency of adverse effects and the recurrence of lesions when treatment is discontinued.

Prognosis and complication

The malignant transformation rate of oral leukoplakia varies from 0 to 33%. Overall, 3 to 8% of leukoplakias develop malignant transformation in a average follow-up period of five years.
Any leukoplakia could transform into a carcinoma, even those which did not show epithelial dysplasia initially (or in which dysplasia happened to be absent from the biopsy taken). The main problem is that the malignant transformation cannot be reliably predicted yet. Nonetheless, some data could help identifying the possible risk. Leukoplakias show a high transformation risk when they: 1.- affect women; 2.- persist for long periods; 3.- appear in non smokers, 4.- are located on the floor of the mouth or tongue; 5.- are seen in patients with a previous head and neck carcinoma; 6.- are non-

homogenous; 7.- are infected by *Candida*; 8.- show epithelial dysplasia, 9.- show DNA aneuploidy. Of all these factors the presence of epithelial dysplasia still seems to be the most important indicator of malignant potential but ploidy may soon be more useful. Some leukoplakias show an increased recurrence rate (proliferative verrucous leukoplakia; PVL). On the other hand, some leukoplakias disappear spontaneously without any specific therapy.
Regular check-up of these patients is essential, probably every 3, 6 and then 12 months, both in treated and untreated patients.

Prevention

There is no known therapy to prevent development of oral leukoplakia and there is no known therapy to prevent oral squamous cell carcinoma developing from oral leukoplakia;.
It has been demonstrated that a healthy life style and the abstinence of tobacco are the best way to prevent both.
Fresh fruits and vegetables may have a protective effect in the primary prevention of oral cancer and precancer.
Early diagnosis and treatment of leukoplakia, can reduce the high rates of oral cancer morbidity and mortality in many countries.
Screening programs for oral cancer and precancer may be indicated in individuals at risk, such as predetermined age (40-70 years), gender (males in some countries), risk habits (tobacco/alcohol users) and in certain geographic areas with a high incidence of oral cancer.

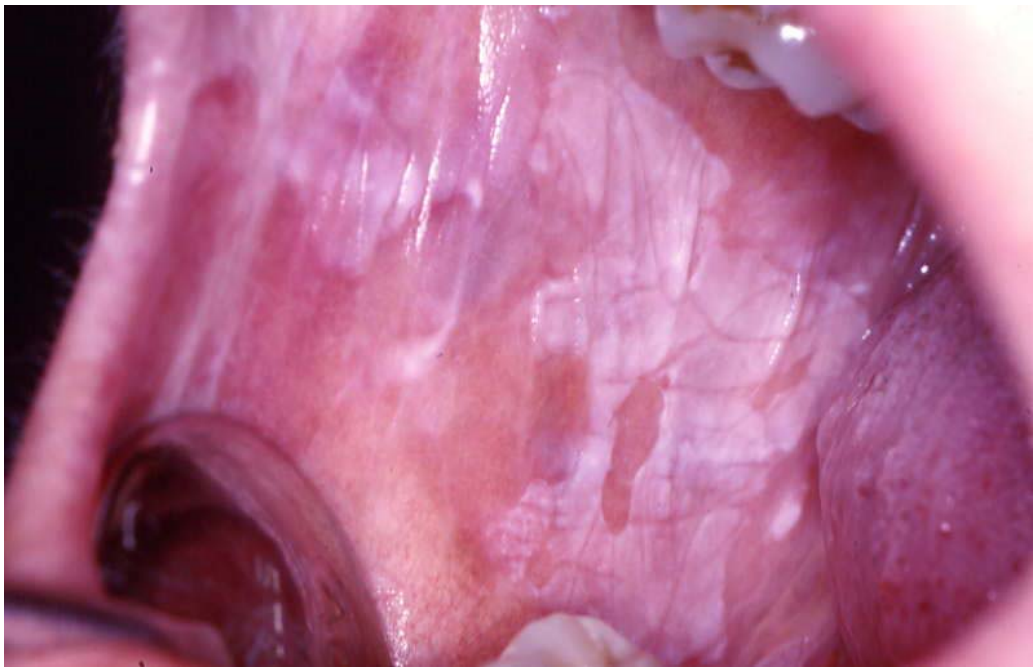

Figure 1. Leukoplakia of the buccal mucosa

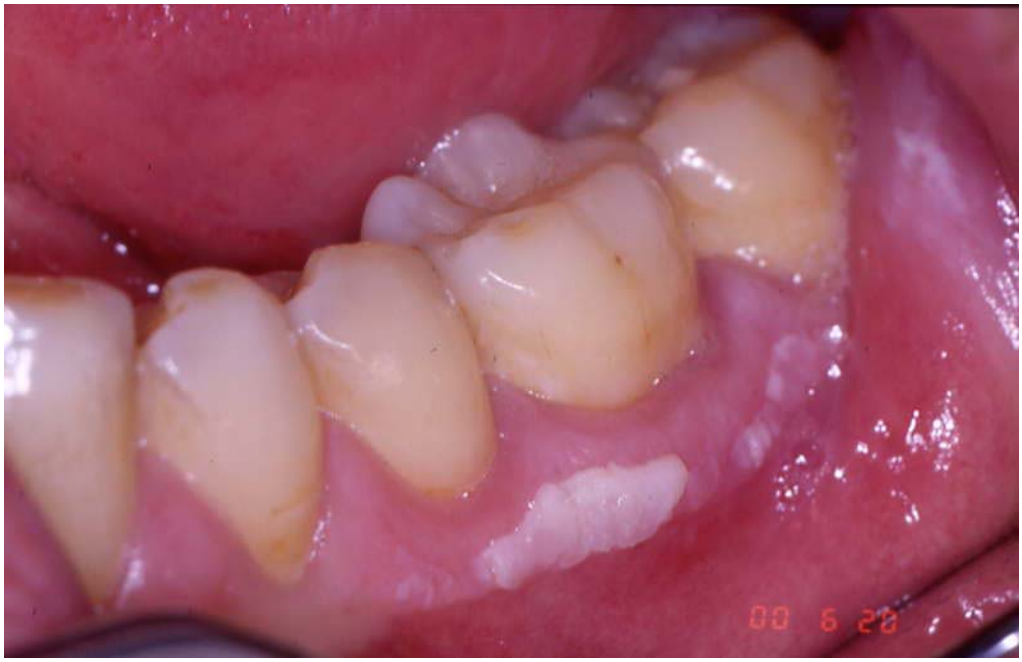

Figure 2. Leukoplakia of the gengiva

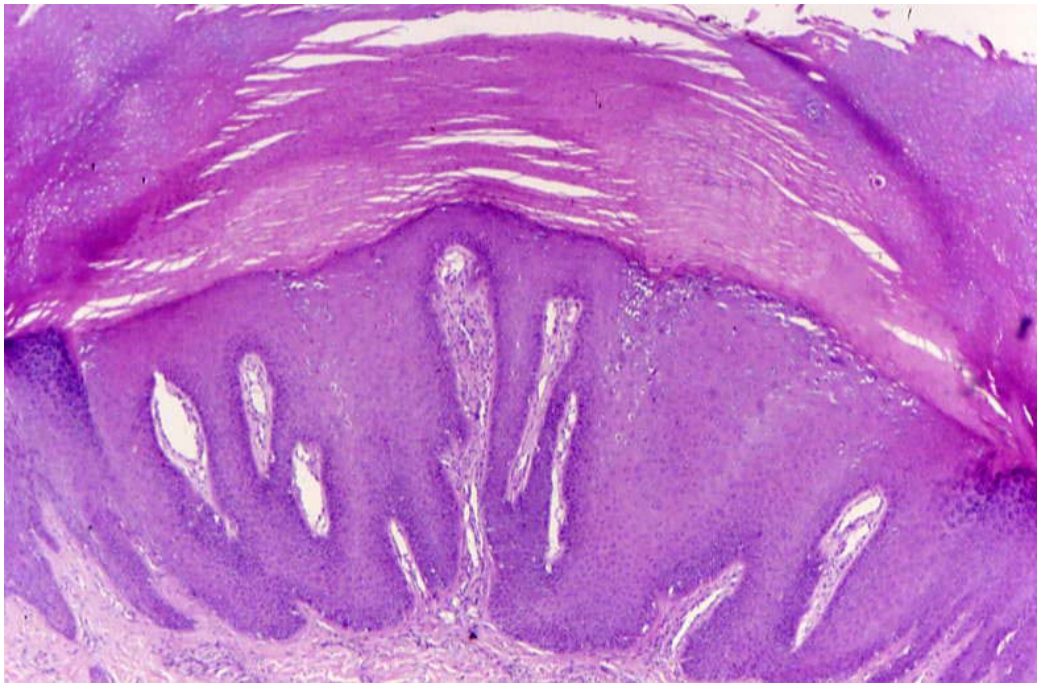

Figure 3. Leukoplakia, histological aspect

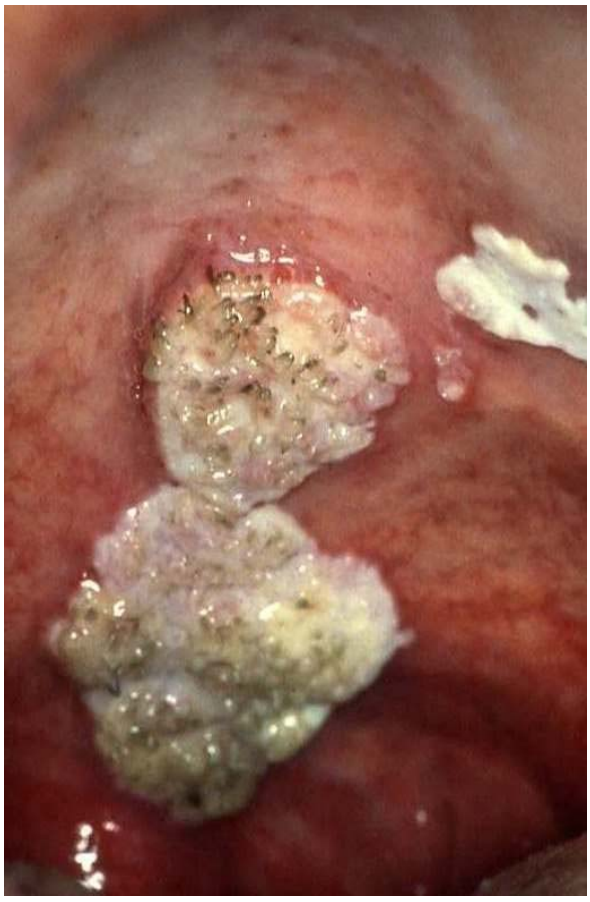

Figure 4. Leukoplakia, verrucous variant

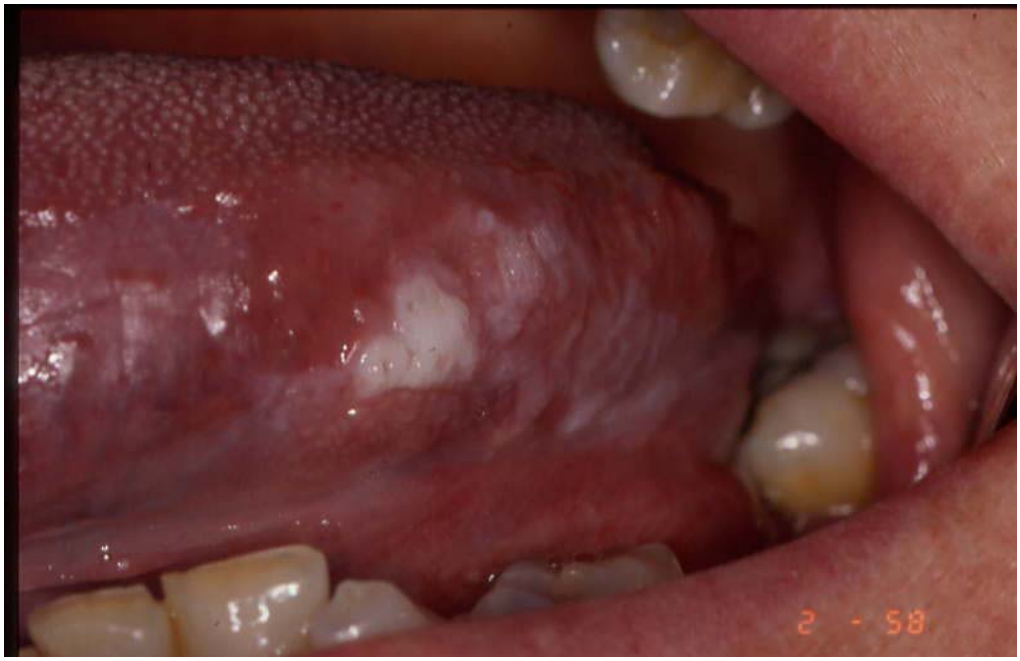

Figure 5. Leukoplakia of the lateral tongue

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Links

www.update-software.com/cochrane

www.emedicine.com/derm/topic227.htm

www.maxillofacialcenter.com/precancer.html

MUCOSITIS

Definition

Mucositis is an inflammatory-like process of the oral mucosa due to radiation in head-neck oncology patients or chemotherapy.

It is characterised by atrophy of squamous epithelial tissue, vascular damage, and an inflammatory infiltrate concentrated at the basement region. Epithelial atrophy is followed by ulceration.

Mucositis is scored in four grades, I, II, III, and IV, for evaluation of treatment strategies and for communication purposes between oncologists. Grade III and IV mucositis is considered as severe, is painful and is characterized by ulcerative lesions, covered by fibrinous-inflammatory (pseudomembranous) exudate. The term “ulcerative/pseudomembrane mucositis” or the term “pseudomembranous mucositis” is used to describe these ulcerative lesions. Severe mucositis is a costly and dose-limiting complication of chemotherapy and head and neck radiotherapy. Pain and dysphagia (restriction of oral intake) due to severe mucositis may further debilitate the already compromised cancer patient, while the loss of epithelial integrity will serve as site for secondary local infection and as portal of entry for the endogenous oral flora.

Mucositis is considered to be an inevitable but transient side effect of anti-neoplastic therapies.

Epidemiology

During a course of curative radiation, about 80% of the patients will develop different grades of mucositis. In radiotherapy mucositis is an integral part in terms of morbidity, as during a course of curative radiation the majority of patients will develop pseudomembranous mucositis. The early radiation reaction causes local discomfort as well as difficulties in drinking, eating, swallowing and speech.

Hyperfractionation, accelerated fractionation and radiochemotherapy, although especially successful for the treatment of rapidly dividing tumours, result in higher rates of acute toxicity, especially mucositis. In head and neck radiotherapy these more aggressive regimens have been shown to improve local tumor control, but these are related to an increase in severe mucositis. This higher rates of acute toxicity result in higher levels of pain and difficulty in oral intake, and a significant worsening of the patient’s quality of life. Recent data have shown that more than half of the head and neck cancer patients (56%) who receive altered fractionation radiotherapy, will experience more severe mucositis as compared to 34% of patients who receive conventional radiotherapy.

Severe mucositis can give rise to nutritional problems, while hospitalisation and nasogastric feeding may become necessary. Rates of hospitalisation due to severe mucositis, reported in several studies, were 32% for altered fractionation radiotherapy and overall 16% of all types of

radiotherapy. Furthermore, about 10% and up to 30% of patients, depending mostly on the type of treatment, may necessitate an interruption or a modification and prolongation of the course of radiotherapy because of severe mucositis. Interruptions and prolonged treatment adversely affect outcome and therapeutic effect.

In chemotherapy, the incidence and severity of mucositis is influenced by the type of anti-neoplastic drugs and related to tumour type. Based on these factors, between 20-100 % of the patients will develop severe mucositis during chemotherapy. In cancer chemotherapy severe mucositis will dramatically influence oral functions and general condition of the patient. Pain, sometimes requiring intensive analgesia, and restriction of normal feeding and drug intake are most important discomforts. In severe mucositis, secondary infection of the mucosal ulcers can provide a port of entry for micro-organisms into the circulation, leading to life-threatening septicaemia in myelosuppressed patients.

Clinical presentation

The first clinical signs of radiation-induced mucositis occur at the end of the first week of a conventional seven-week radiation protocol (daily dose of 1.8 to 2.0 Gy, five times a week). A white discoloration of the oral mucosa, which is an expression of hyperkeratinisation of the epithelium, followed by erythema, is initially seen (figure 1). In other cases, a white discoloration maybe observed in combination with areas of erythema or erythema may appear first. The above clinical signs represent the grade I mucositis and are mostly asymptomatic. Towards the end of the second or around the third week of radiotherapy, small foci of ulceration can be observed, corresponding to the grade II mucositis. Patient complains of mild pain and can take soft diet. Severe, grade III mucositis presents as ulcers covered by pseudomembranes, affecting large areas of the oral mucosa (figure 2). Pseudomembranes are very painful to rub off, while the patient complains of severe pain and dysphagia (difficulty in oral intake) and can take liquids only. Grade IV mucositis represents even more severe ulceration, covering almost all mucosal surfaces. Patient complains of severe pain, can take liquids only or may necessitate nasogastric tube or parenteral support.

Mucositis is most severe in the soft palate, followed by the mucosa of the hypopharynx, floor of the mouth, cheek, base of the tongue, lips, and dorsum of the tongue. Patients with compromised oral mucous membranes secondary to alcoholism and/or excessive smoking exhibit the most severe mucosal lesions.

Mucositis generally persists throughout radiotherapy, and develops at its maximum grade at the end of the irradiation period. One to three weeks or more, depending on the severity, are needed for mucositis to heal, after the completion of radiotherapy.

Erythematous, ulcerated and xerostomic (dry) oral mucosa serves as site for the development of secondary infection. About one out of three patients are anticipated to develop

pseudomembranous candidosis during radiotherapy. The local inflammatory reaction caused by candidosis adds to the radiation-induced inflammatory process. According to some preliminary literature data, herpes virus-1 reactivation and infection may also complicate oral radiation-induced mucositis, aggravating the ulcerations (figure 3).
Chemotherapy-induced mucositis, initially seen between 3 and 7 days, after infusion of the anti-neoplastic drugs, presents as atrophy, followed by ulcerations within a few days. The maximum grade of mucositis is observed usually after 11 days, and could last for several days to weeks. Secondary local infection will delay healing.

Aetiopathogenesis

Mucositis is basically a tissue reaction to the trauma of radiation or chemotherapy. Total dose, radiation portals, fractionation schedule, and type of ionising radiation as well as dose and type of chemotherapy agents affect the occurrence and severity of mucositis.
The pathogenesis of mucositis, being similar but not identical in both chemotherapy and radiation, is not fully understood.
The hypothesis proposed for the development of radiation- and chemotherapy-induced mucositis consider four consecutive phases: (1) inflammatory/vascular phase (free radicals and cytokines are released); (2) epithelial phase (reduced epithelial renewal-atrophy); (3) ulcerative/bacterial phase (colonisation by mixed flora, causing release of endotoxins, with further tissue damage by stimulation of cytokines). An interplay between the radiation- or chemotherapy-induced epithelial ulceration and bacterial flora is implied in this phase; (4) healing phase.
Factors that may contribute to the development of mucositis include the increase in inflammatory mediators, platelet activating factor in saliva, leukocyte adhesion to E-selectin or endothelial intercellular adhesion molecule-1 (ICAM-1) which promotes the radiation-induced inflammatory response in squamous epithelium, a decrease in the level of salivary epidermal growth factor and loss of protective salivary constituents.
A marked increase in the carriage rate of Gram-negative bacilli in the oropharynx (a/o. *Enterobacteriaceae, Pseudomonaceae*) has particularly been shown as a possible aggravating factor in the development of oral mucositis. Selective elimination of Gram-negative bacilli was associated with a reduction of radiation-induced pseudomembranous mucositis.
The most common infection in the oral cavity during or shortly after radiotherapy and chemotherapy is candidosis. Many patients become colonised intra-orally with *Candida albicans* during cancer therapy. The prevalence of positive *Candida* cultures increased from 43% at baseline to 62% at completion of cancer therapy and to 75% during the follow up period. Some believe that oral mucositis is aggravated by fungal infections. However, treatment of yeast and

Gram-positive cocci with topical anti-fungals and disinfectants failed to relieve such complications. Thus, many of the oral lesions observed during treatment do not seem to be due to candidosis or streptococcal infection. Finally, it should be mentioned that herpes simplex virus infection is not a significant contributing factor in irradiation mucositis, this is in contrast to the commonly seen herpes simplex virus reactivation following chemotherapy and radiochemotherapy patients.

The direct toxic effect of cytostatic agents on rapidly dividing cells of the oral epithelium result in atrophy, erythema and ulceration. Indirect stomatotoxic effects are caused by release of inflammatory mediators, loss of protective salivary constituents, and therapy induced neutropenia, in combination with the colonisation of bacteria, fungi and viruses on damaged mucosa which can result in secondary infections. Neutropenia, in chemotherapy, increases the risk for secondary infections.

Diagnosis

The diagnosis of grade I mucositis is based on the presence of asymptomatic mucosal erythema, evaluated on clinical grounds, and need no treatment. It has to be differentiated from erythematous candidosis, a common infection during head and neck radiotherapy and antineoplastic chemotherapy, which needs antifungal treatment. The differentiation of mucositis from the infection can be done only on clinical grounds. Laboratory findings of a positive *Candida* smear do not assist in the differential diagnosis, given the high *Candida* spp. carriage level (up to 75%) of patients during antineoplastic therapies. Symmetrical erythemas, erythema located only on the central area of the dorsum of the tongue or bilateral angular cheilitis may denote the presence of candidosis.

Grade II mucositis, with small foci of ulcers, is also diagnosed upon the clinical presentation, while it has to be differentiated from an early intraoral herpetic infection or from a superimposed candidosis.

The most distressing grade III and IV mucositis is diagnosed upon its clinical presentation of superficial ulcerations covered by pseudomembranes (figure 4), that are very painful to be rubbed off. These pseudomembranous ulcerations are to be differentiated from pseudomembranous candidosis (figure 5), consisting of whitish, easy to rub off, pseudomembranes. Again, the laboratory isolation of yeasts from smears, taken from the lesions, may be helpful, but is not critical for the diagnosis. Pseudomembranous candidosis may be superimposed on the pseudomembranous ulcerations of mucositis and, in these cases, the differentiation is difficult.

Severe mucositis is important to be differentiated from the, often clinically identical, herpes simplex virus-1 reactivation and infection in neutropenic patients. Herpetic infection, if not diagnosed and treated promptly, may further aggravate mucositis and delay healing, thus

compromising the antineoplastic protocol (figures 6 - 7). Early initiation of ulcerative mucositis or herpes labialis may assist in suspecting a herpetic infection.

Treatment

The Consensus Development Panel of the National Institutes of Health (Consensus statement, 1990) stated that no drugs can prevent mucositis, an opinion that still holds to date, though the evidence is that ice cooling can minimise chemotherapy-induced mucositis.

Consequently, treatment of mucositis is still limited to reduction of its severity. Oral care programs, relief of pain and discomfort, early diagnosis and treatment of concomitant secondary mucosal infections and/or strategies to eliminate micro-organisms, that are thought to promote or aggravate mucositis, are all engaged in its treatment.

For relief of pain and discomfort due to mucositis several anaesthetics, analgesics, and mucosal coating agents, acting as cytoprotectants, have been recommended.

Periodic rinses with topical anaesthetics such as viscous xylocaine (lidocaine) and benzydamine are often proposed. For relief of pain and resolution of mucositis, encouraging results have also been reported with the use of sucralfate suspensions, thought to form a protective barrier on the oral mucosa.

Antibacterials are also used to reduce mucositis. The potential beneficial effects of aqueous chlorhexidine rinses to control chemotherapy-associated oral mucositis has been reported, but it did not seem to control radiation mucositis. Besides, it may cause mucosal burning and irritation. Selective elimination of oral Gram-negative bacilli has been shown to have an ameliorating effect on the severity of radiation mucositis. The use of polymyxin E/ tobramycin/ amphotericin B (PTA)-containing lozenges, pastilles or paste were shown to reduce mucositis.

Preliminary research data indicate that the administration of growth factors (granulocyte-macrophage colony stimulating factor, keratinocyte growth factor) and radioprotectors may reduce the severity of mucositis and promote healing. The reduction of mucositis and promotion of healing by growth factors is most likely due to stimulation of surviving stem cells, but this needs further study especially as these therapies may affect tumour response. This consideration is also applicable to the administration of the radioprotective agent amifostine during radiation treatment. A major flaw of most of the preliminary growth factor and radioprotector studies is that their trial design is at least questionable and the outcomes subject to debate. Nevertheless, the results of these preliminary studies are promising and may finally lead up, after repeated in high-quality randomised, placebo-controlled clinical trials, to modification of current oral care programs that are of limited efficacy in treating radiation mucositis.

Prognosis and complication

Severe, grade III and IV mucositis causes pain and dysphagia and may debilitate the already compromised cancer patient. However, mucositis usually heals within one month after the completion of antineoplastic chemotherapy and head and neck radiotherapy, leaving no other significant side effect, and, thus, having a good prognosis.

Severe mucositis gives rise to nutritional problems, and may necessitate hospitalisation and nasogastric feeding, increasing the cost of antineoplastic therapy, while it seriously affects patient's quality of life.

The development of secondary local and systemic infection, which may threaten life in immunocompromised patients, is an important complication related to mucositis. Constant surveillance of the patient, with early and prompt diagnosis and treatment of the infection will minimize the effect of the above complication.

Another, most important complication of severe mucositis is its dose-limiting effect, the modification, the interruption or the prolongation of the antineoplastic therapy, adversely affecting the outcome and therapeutic effect.

Prevention

Mucositis is, at present, an inevitable side effect of antineoplastic therapies. Several strategies, including oral care programs and improved radiation treatment modalities, are available to prevent or reduce the incidence and the severity of mucositis.

Currently, most oral care programs aim at: removal of mucosal irritating factors, cleansing of the oral mucosa, maintaining the moisture of the lips and the oral cavity, relief of mucosal pain and inflammation. Although it has been suggested that good oral hygiene may reduce the development and severity of mucositis, no controlled studies of large numbers of patients have been undertaken yet. Nevertheless these recommendations still are a part of most protocols aimed to reduce the oral sequelae of head and neck radiotherapy and chemotherapy. To prevent iatrogenic mucosal damage, irritating factors such as sharp or rough fillings should be smoothened or polished prior to cancer therapy, and prosthetic appliances should be closely evaluated. Plaque control and oral hygiene should be maintained. Some recommend discouraging the wearing of dentures during radiotherapy. As denture surfaces may be colonised with *Candida* species, others recommend special attention to denture hygiene and removal of the appliance at least at night. In keeping with the scope of the elimination of irritating factors, the use of tobacco, alcohol, and spicy and acidic foods should also be discouraged. Patient should be instructed to take soft diet.

The use of various radiation treatment modalities and schedules of fractionation can play an important role in the prevention of mucositis. The use of high-energy photon beams, with the linear accelerators, provides a more homogenous dose distribution in and outside the target

area compared to the orthovoltage technique. This is due to the higher penetration of high-energy beams. Accelerated fractionation results in a more rapid onset of mucositis.
Early diagnosis and treatment of local infections, such as candidosis, and herpetic infection or infections due to Gram-negative bacilli, will benefit mucosal inflammation and minimize ulcerative lesions.

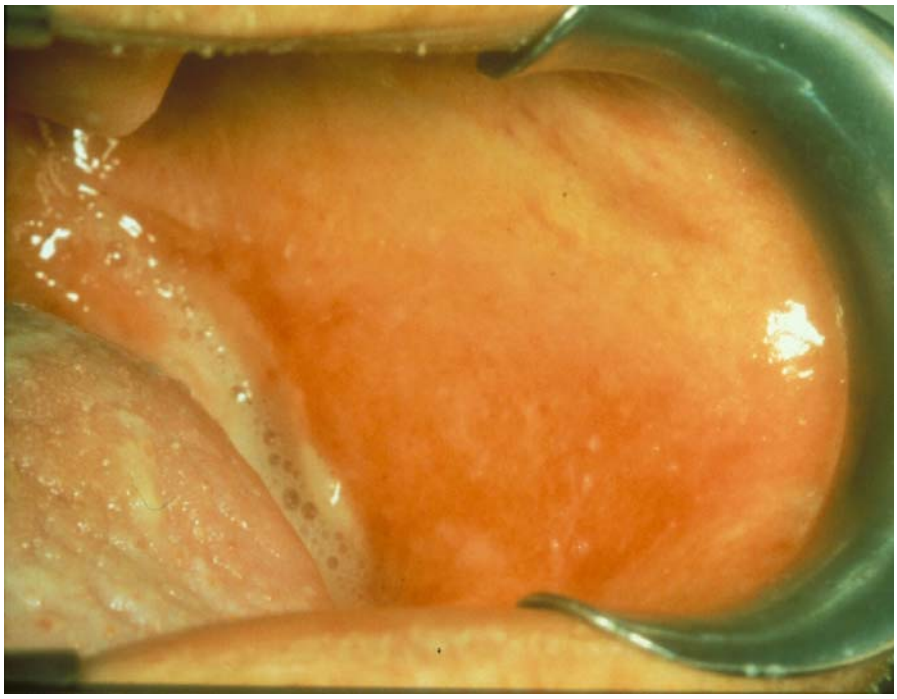

Figure 1. Grade I mucositis with erythematous changes of the left cheeck mucosa. The demarcation between radiated and non-irradiated tissue is obvious.

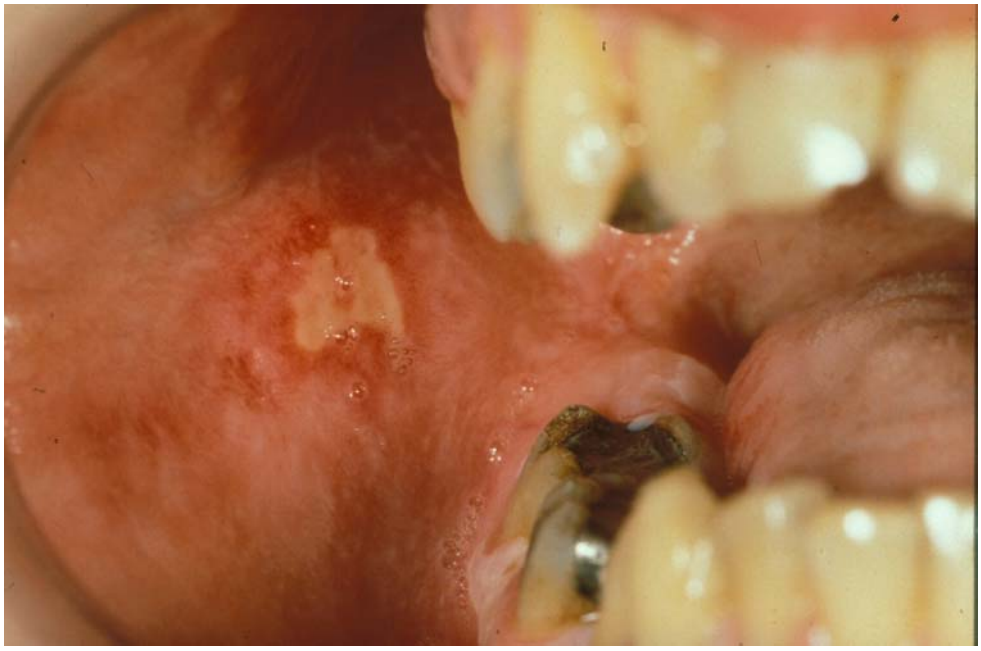

Figure 2. Grade III mucositis (paiful superficial ulcers covered by pseudomembranes) on the buccal mucosa of a 55 year old male (4th week of radiotherapy, 26 Gray, for the treatment of a squamous cell carcinoma of the tongue). (Viral culture for herpes simplex virus-1 infection was negative).

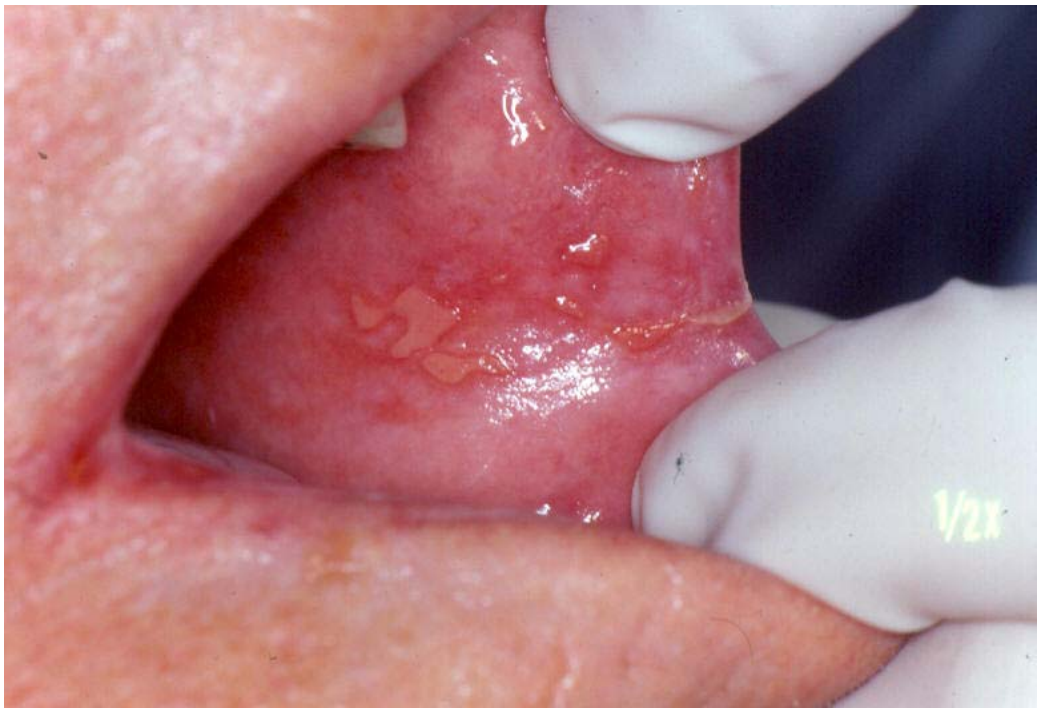

Figure 3. Painful superficial ulcers covered by pseudomembranes, clinically identical to grade II mucositis, on the buccal mucosa of a 74 year old male (7th radiotherapy fraction, 14 Gray, for the treatment of an oral squamous cell carcinoma). Viral culture and cytology smear were positive for herpes simplex virus-1 infection. Patient responded well to antiviral treatment and ulcers were diagnosed as of herpetic etiology. Radiotherapy was not interrupted.

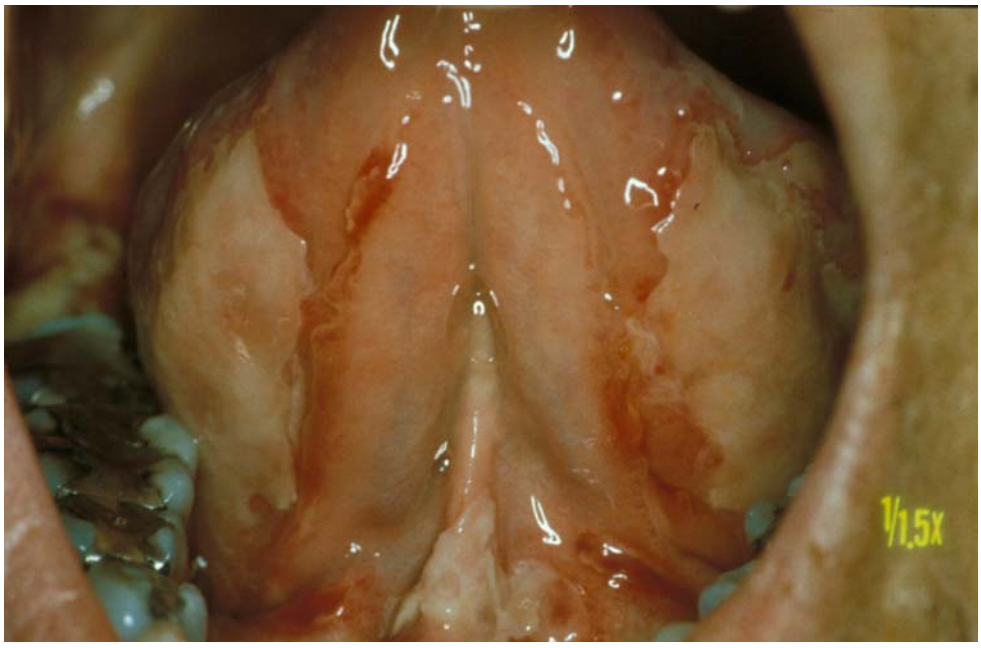

Figure 4. Grade III mucositis (painful superficial ulcers covered by pseudomembranes) on the lateral borders of the tongue and floor of mouth of a 28 year old female during chemotherapy (9 days after infusion) during an autologous bone marrow transplantation.

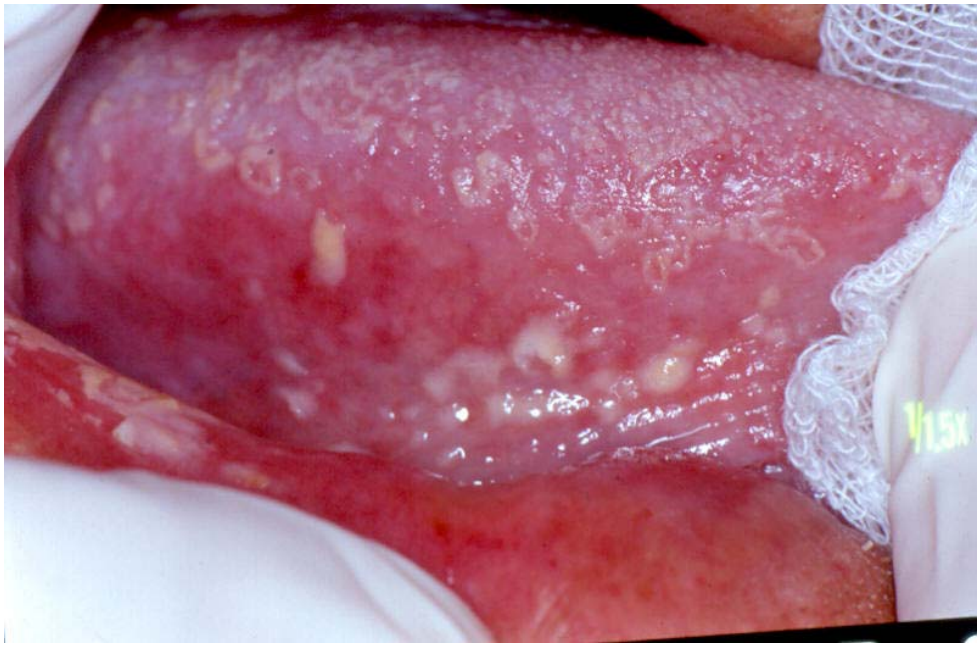

Figure 5. Pseudomembranous candidiasis (whitish-yellowish candidal pseudomembranes) on the tongue and buccal mucosa (30th fraction of radiotherapy for the treatment of a squamous cell carcinoma of the floor of mouth). Patient complained of xerostomia and bad sensation, no pain.

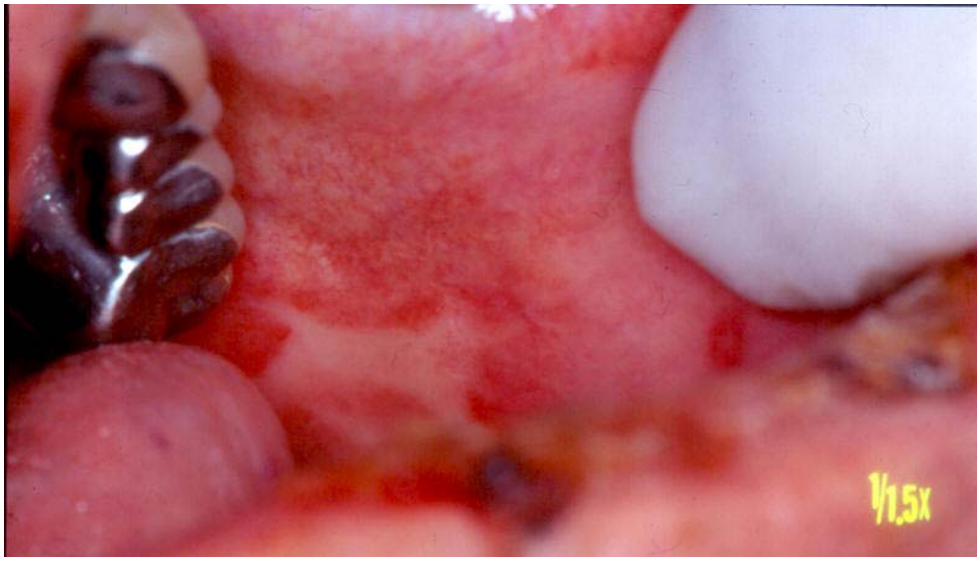

Figure 6. Painful ulcerations, covered by pseudomembranes, clinically identical to grade III mucositis, on the buccal mucosa of a 67 year-old male with a non Hodgkin's lymphoma, 17 days after induction chemotherapy. Lesions were not healing, delaying the administration of the next chemotherapeutic scheme.

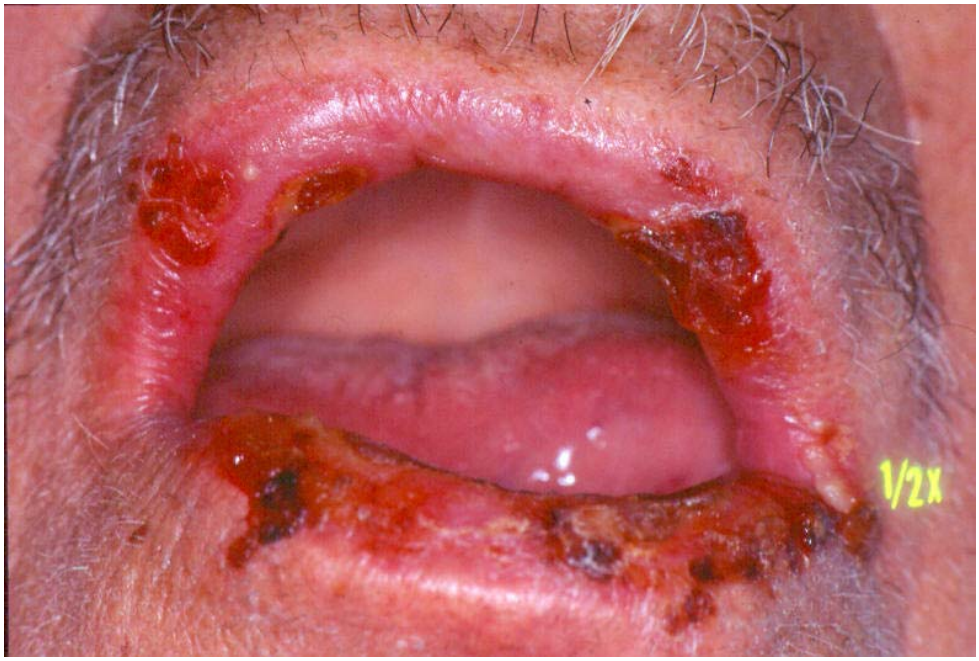

Figure 7. Same patient, as in figure 6. Multiple, haemorrhagic ulcerations and crusting on the lips. Cytology showed a herpetic infection and patient responded well to intravenous antiviral treatment.

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NECROTIZING SIALOMETAPLASIA

Definition

Necrotizing sialometaplasia was first described in 1973 by Abrams, Melrose and Howell and a further five cases were reported the following year by Dunlap and Barker. It is a rare, self limiting, variably ulcerated, benign, inflammatory process, predominantly affecting salivary tissue. The importance of the lesion is that it may be mistaken for a malignancy and lead to inappropriately radical surgery. A famous dignitary, President Clevelend of the United States of America, may have suffered from this disease. The entity is classified under “tumour-like” in the WHO Classification of tumours of the salivary glands.

Epidemiology

Necrotizing sailometaplasia is extremely rare: there are barely 200 cases reported in the world literature.

Mean age of occurrence in men is about 50 years and 36 years in women. The youngest reported case is 15 years. There appears to be an increased incidence in males. A preponderance for Caucasians reported by Lynch et al (1979) was thought to be spurious, but in Brannon’s series of 69 cases compared to 115 in the literature in 1991, there was a 5:1 preponderence of Caucasians over Afro-Carribeans.

The vast majority (80%) of cases affect the minor salivary glands of the palate, while other sites include retro-molar pad, gingiva, lip, tongue and cheek. The condition has also been reported in major salivary glands. A sub-acute variant has also been described.

Clinical Presentation

Clinically, patients present with a rapidly-growing swelling, which may (or may not) ulcerate, usually in the palate. Ulceration does not occur in the sub-acute variant which has been described. A purulent exudate may be an early feature at the site of the lesion. Pain may also be a feature at the onset and may be intense and referral of the pain to the ear, eye and pharynx are variable features which have been reported. However, development of the lesion may be painless and there are even reports of anaesthesia of the greater palatine nerve as the presenting feature. This is thought to be caused by involvement of the vasa nervorum in the vasculitic aetiological process. The lesions may

occur bilaterally and metachronously. When ulceration occurs, it usually remains superficial, but a single case of full-thickness necrosis of the palate has been reported. The lesion heals spontaneously over a period of two to twelve weeks. Drug therapy with intra-lesional steroids appears to offer no benefit on recovery time of the lesion or associated anaesthesia.

A sub-acute variant of the condition has been described in which the lesions are usually painful, ulceration is not present and histopathology demonstrates a sub-acute inflammatory infiltrate. However, these cases may simply represent one end of a spectrum of disease.

Differential diagnosis of an ulcer presenting with these features could include: direct traumatic ulceration, major aphthous ulceration, syphilis, tuberculosis, deep mycosis, agranulocytosis, neutropaenia and nicorandil-induced oral ulceration. The most important differential diagnosis, is malignancy, in particular squamous cell carcinoma, low-grade mucoepidermoid carcinoma and oncocytic malignancies.

Rarely, the condition has also been reported at extra- salivary sites, which include: the nose, nasopharynx, trachea, larynx and lung. At extra-salivary sites, the lesion may be described as adenometaplasia. A similar lesion occurs in the skin termed syringometaplasia, and similar histopathological appearances have been described in the breast following trauma.

Aetiopathogenesis:

Although the aetiopathogenesis of necrotizing sialometaplasia remains unknown there is general consensus that an ischaemic event in the salivary gland precedes the development of the lesion. In experimental models, ligation of the arterial supply to major salivary glands in rodents may result in a similar histopathological picture and similar lesions may also occur spontaneously in dogs and experimentally in rabbits and rats. The disease has been reported in patients with sickle cell disease, where infarction may be a feature in crisis, Buerger’s disease and Raynaud’s phenomenon, vasculopathies which both predispose to ischaemia. It has been suggested that necrotizing sailometaplasia of the palate may represent an ulcerative or necrotizing stage of leukokeratosis nicotina palate, although this now seems unlikely.

Other predisposing factors in which ischaemia may play a part include: smoking (and alcohol), vascular damage due to trauma, hot food, intubation, fellatio, bronchoscopy, local anaesthetic injection and recurrent vomiting. Addition of a vasoconstrictor to local

anaesthetic solutions, local radiotherapy, cocaine use, pressure from local space occupying lesions and surgery have also been implicated. The lesion may be more florid in pregnancy.

There may be an association with other tumours, specifically: Warthin's tumour, Abrisokov's tumour, carcinoma of the lip, rapidly growing mesenchymal malignancy and salivary gland tumours. There is also an association with preceding upper respiratory tract infection within the previous few weeks, particularly acute on chronic sinusitis and allergy. It is possible that the ischaemic event in these cases is due to immune complex disease, similar to the aetiology of erythema multiforme or benign trigeminal sensory neuropathy.

Histopathology

The histopathological features and differential diagnosis of necrotizing sialometaplasia have been reviewed by many authors since the original description by Abrams Melrose and Howell in 1973.

The condition is characterized histopathologically by ischaemic lobular necrosis of sero-mucinous glands with maintenance of intact lobular architecture despite coagulative necrosis of the mucinous acini. Pale acinar outlines often persist, but the nuclei are hypochromatic or absent. Mucin extravasation into the adjacent tissues evokes an inflammatory reaction dominated by histiocytes and granulation tissue. Within the necrotic lobules the inflammatory component is often minimal, but is usually prominent in the surrounding tissues. Although squamous metaplasia of ducts and acini is a feature, (which complicates the diagnosis due to similarity to malignancy) the metaplastic cells have benign nuclear morphology, with minimal pleomorphism or hyperchromatism and few mitotic figures. Nests of squamous epithelium usually with a smooth periphery may be seen, which occasionally have an irregular outline. Pseudoepitheliomatous hyperplasia, where the overlying or adjacent epithelium is often markedly hyperplastic with thick elongated and complex rete processes, along with extensive ductal metaplasia may resemble epithelial malignancy and in the past, misdiagnosis may have let to inappropriate radical ablative surgery. It may be very difficult to distinguish necrotizing sialometaplasia from squamous cell carcinoma, low-grade mucoepidermoid carcinoma and oncocytic tumours.

Specific histopathological features may have some relation to the age of the lesion at biopsy. Coagulative necrosis is a more dominant feature in the early lesions, whereas

fibrosis and squamous metaplasia are features of an older lesion. Anneroth and Hansen suggested that the following five stages occur in most cases: infarction, sequestration, ulceration, repair and healing.

Management

The usual management of this condition is simple observation until the healing phase is complete. Necrotizing sialometaplasia may occur de novo, after trauma or a surgical procedure or in association with another lesions, either benign or malignant.
Because of the latter, whenever the diagnosis of necrotizing sialometaplasia is made, close follow up is indicated until healing is complete. Recognition of the histological picture and the varied clinical settings in which necrotizing sialometaplasia can be found is essential, to avoid histopathological misinterpretation and inappropriate treatment for this benign reactive condition. The prognosis is excellent, once the correct diagnosis is made. There are no known preventative strategies.

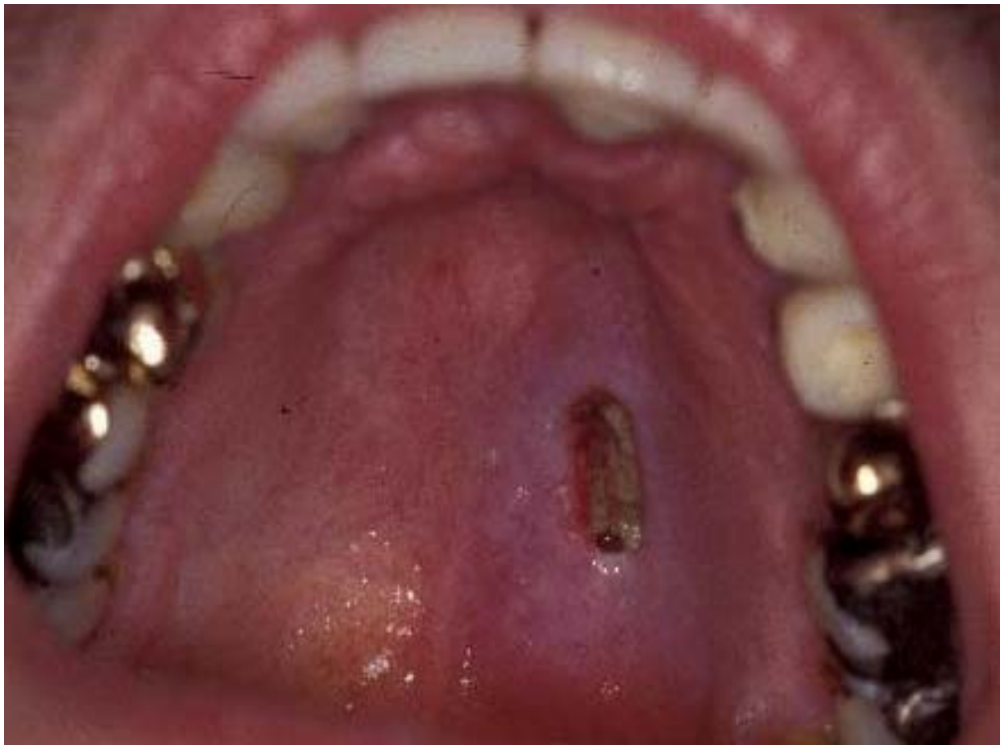

Figure 1. Necrotizing sialometaplasia at the typical site. The ulceration is full-thickness, deep and there has been involvement and exposure of the underlying bone.

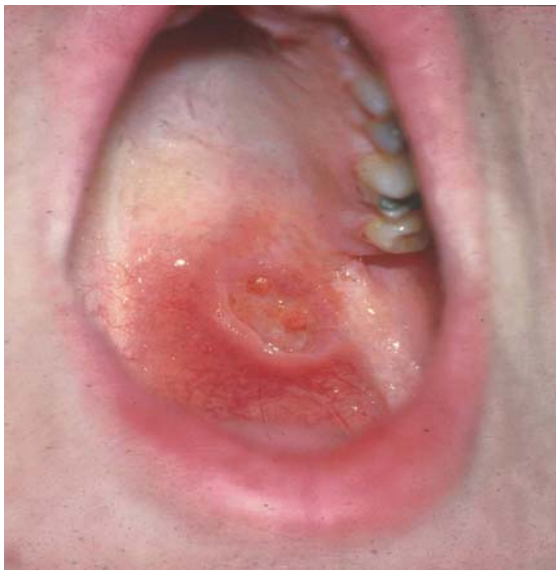

Figure 2. This lesion is more superficial. The clinical similarity to squamous cell carcinoma is obvious. Note, however, the surrounding inflammatory erythema.

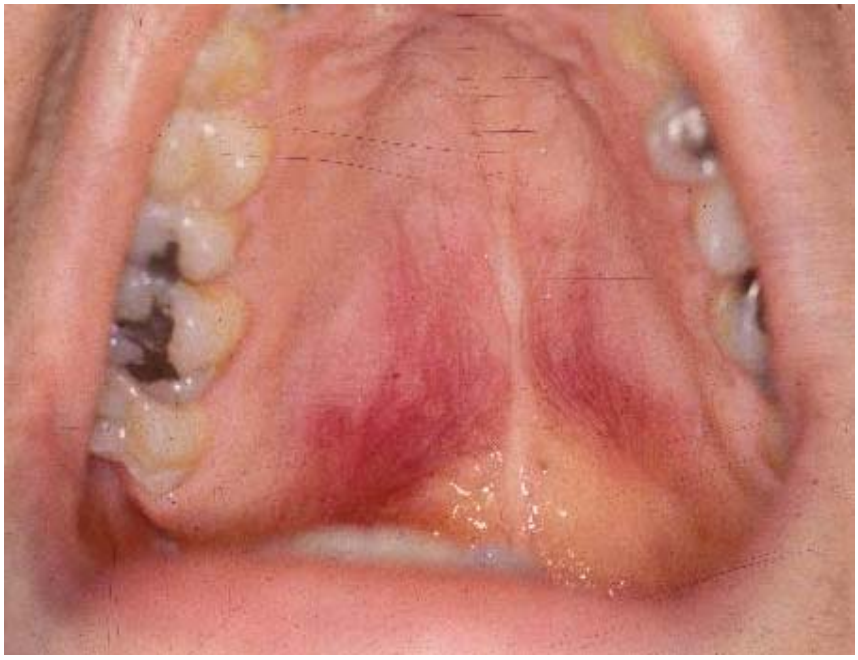

Figure 3. The sub-acute variant, unusually occurring bilaterally (note erythema also). Biopsy confirmed necrotizing sialometaplasia, but the lesions did not ulcerate.

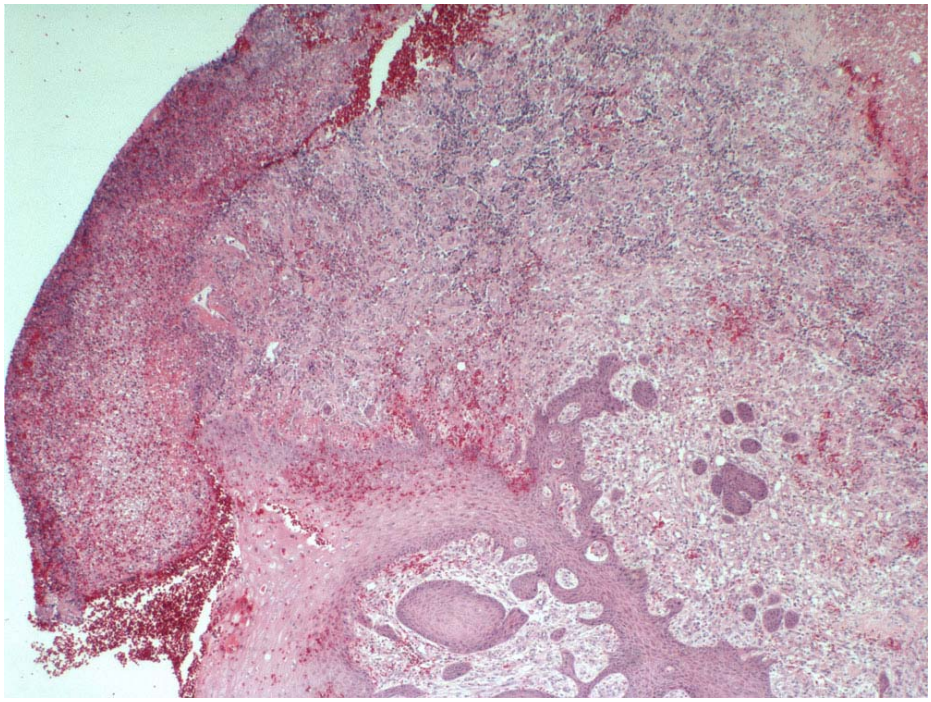

Figure 4. Ulcerated lesion with squamous proliferation at edge of ulcer.

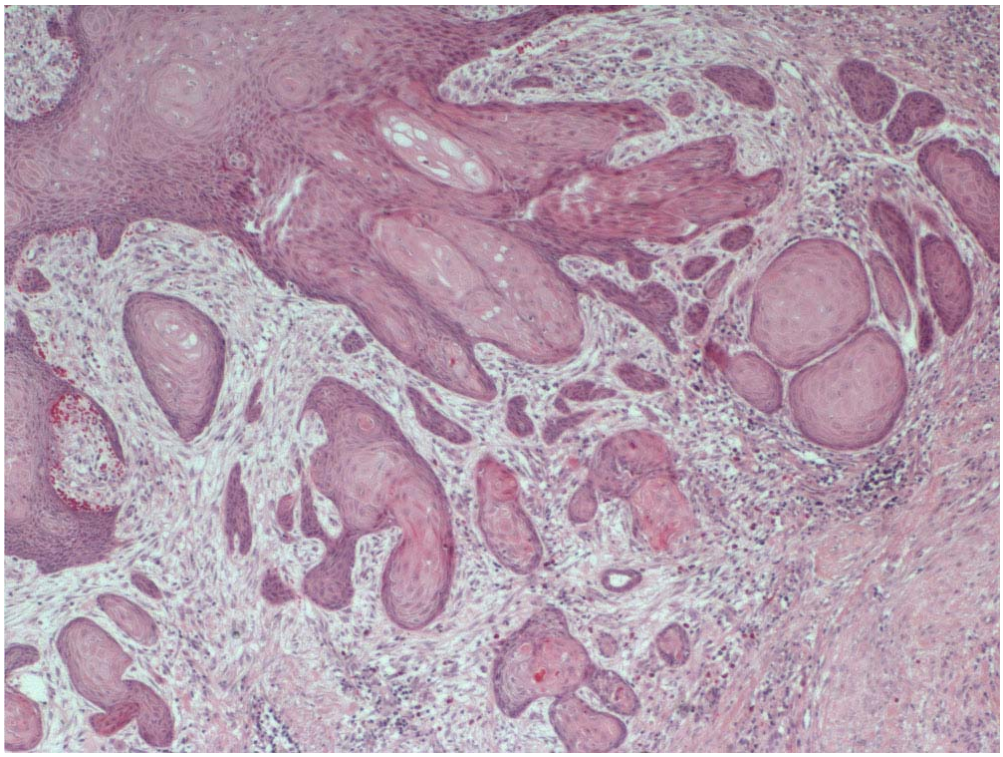

Figure 5. Note extent and worrying complex architecture of squamous proliferation.

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OBSTRUCTIVE SALIVARY DISEASE

Introduction

The salivary glands can be affected by a wide variety of clinical conditions. However, the vast majority can be classified on the basis of the nature of their complaint into:

- Obstructive salivary disease
- Dry mouth
- "Lumpy"
    - whole gland (possible underlying systemic condition)
    - part gland (possible tumour)

Definition

Obstructive salivary disease can occur mainly as a result of:

Sialolithiasis

Strictures

Mucocoeles and salivary cysts

Sialolithiasis

This is a chronic and recurring disease, which may cause symptoms by:

- swelling of glands
- decrease of salivation
- increased viscosity of saliva
- inflammation
- salivary gland “colic”

Strictures

Strictures of a salivary gland duct occur either as a complication of a pre-existing calculus, mucous plugs or following trauma to the duct wall. Such trauma may be the result of cheek biting, overextended denture flanges, damage during dental procedures, following surgery in the region or as a result of assaults or accidents.

Mucocoeles and salivary cysts

Salivary retention or extravasation cysts commonly occur following trauma to minor salivary glands or their ducts. They can occur anywhere in the oral cavity where there are minor salivary glands but the lower lip and posterior buccal mucosa are the

common sites as cheek and lip biting are usually the cause. Lichen planus predisposes to *superficial* mucoceles.
A ranula is a similar cyst arising in the floor of mouth from the sublingual gland. Rarely, congenital cysts of the major salivary glands are seen. A sialocoele may arise in a major salivary gland following obstruction or previous surgery. Multiple cystic changes in a major salivary gland can occur bilaterally in HIV positive patients.

Epidemiology

Sialolithiasis

This is a common finding, accounting for 50% of major salivary gland disease. Post mortem studies suggest that the prevalence of salivary calculi is approximately 1.2% of the population. However, the prevalence of symptomatic salivary calculi may be 0.45%. There is a slight male preponderance, and the peak incidence is between the ages of 30 and 60. They grow by deposition and range in size from 0.1mm to 30mm. The commonest site is the submandibular gland where 80-90% of calculi are found, 5-10% are found in the parotid gland and approximately 5% in the sublingual and other minor salivary glands. The majority are formed from phosphate and oxalate salts with a clear distinction between submandibular and parotid stones both in frequency and composition. Parotid gland stones contain more acidic mineral phases, such as brushite and octacalcium phosphate and contain about 70% more organic matrix, 40% more protein and 54% more lipids. The organic matrix of submandibular stones, however, is richer in protein and has a higher (13%) content of lipids.

Strictures

These are a small but important cause of obstruction of the duct. Parotid duct strictures are a more common sialographic finding than submandibular duct strictures and account for up to 25% of recurrent parotid gland swellings.

Mucocoeles and salivary cysts

The majority of mucocoeles (80%) occur in patients below the age of 40 years, with the peak incidence in the 10-20 year age group. The site most commonly affected is the lower lip (60-70%) while the floor of the mouth is only involved in 6% - 15% of cases.

Clinical presentation

Obstructive salivary gland disease can cause pain and swelling. The pain is

experienced during salivary stimulation and is intensified at mealtimes, so called “meal time syndrome”. The accumulation of saliva in the gland, duct or surrounding tissues produces `swelling and the area becomes enlarged and firm.

Sialolithiasis

Sialoliths may present acutely as a result of acute bacterial infection secondary to stasis (sialadenitis). In such cases there is often facial asymmetry and the affected gland is painful, hot and swollen. The duct orifice may also be inflamed and pus may be expressed on milking the gland.

More commonly they present with a history of recurrent swelling, which has increased in both frequency and severity over time, particularly at mealtimes. This swelling resolves spontaneously, or with massage over a period of time. Milking of the gland in such cases may reveal a reduced salivary flow from the affected gland. Submandibular calculi situated in the region of the ostium may be visible, while those in the anterior part of Wharton's duct may be easily detected clinically by bimanual palpation. Calculi located in the posterior half of the duct are more difficult to palpate, especially if small, and will require intraoral occlusal radiographs to demonstrate them. Palpation of calculi located within Stensen's duct is more difficult, the bulk of the buccinator and masseter muscles masking the presence of calculi, and detection has traditionally relied on radiography.

Strictures

The presentation is very similar to that of salivary calculi with the difference that no calculus can be palpated. In such cases sialographic examination will be required to confirm the diagnosis.

Mucocoeles and salivary cysts

In the case of mucocoeles there is often a history of trauma following which a swelling slowly develops and increases in size. As it increases in size it may take on a bluish colouration and eventually bursts discharging the contents, which may have a salty taste, before recurring at the original site and repeating the cycle.

A ranula (so named because of the resemblance to the bulging underbelly of a frog) is a mucocoele in the lingual gutter. The fact that these arise from the sublingual gland is demonstrated by the protein and amylase content of the cyst fluid.

Aetiopthogenesis

Sialolithiasis

At present no single theory appears to fully explain the aetiology of salivary calculi. Hence, it is likely that several factors, working in parallel or in series, contribute to the development of a sialolith. The requirements for stone formation are saturation, crystal inhibition, crystal nucleation, growth and aggregation and crystal retention in the ductal system

Saturation

The level of saturation may be altered by pH, dehydration, diet and stagnation. However, at present none have been shown to play a significant role.

Crystal inhibition

Saliva contains a family of calcium binding proteins and it is possible that variations in these may play a role. However, it cannot be a major cause as bilateral and recurrent stones are uncommon.

Nucleation, growth, aggregation

Several factors have been implicated in this area and include bacteria, foreign bodies, cellular debris, infection and the continual and spontaneous formation of microcalculi.

Retention in the ductal system

The cells lining the duct may play a role while simple anatomical factors, such as the mylohyoid bend, long course of the submandibular duct and the fact that the saliva is secreted against gravity should not be overlooked.

Strictures

Strictures of a salivary gland duct occur either as a complication of a pre-existing calculus, mucous plugs or following trauma to the duct wall. Such trauma may be the result of cheek biting, overextended denture flanges, damage during dental procedures, following surgery in the region or as a result of accidents.

Mucocoeles and salivary cysts

Mucocoeles are usually either extravasation cysts (85%) or retention cysts (15%). The former are thought to arise as a result of trauma to the gland or duct and the latter by retention. However, there is probably a combination of the two mechanisms as there is evidence that intraductal cysts result in necrosis and then extravasation.

Diagnosis

In all cases the diagnosis is based on a careful history, clinical examination supported by the relevant special investigations. As the history and clinical findings

have been discussed under the section on clinical presentation we will limit this section to the special investigations, which will confirm the diagnosis.

Special investigations

Traditionally, plain radiographs are often used as a simple first line investigation. This has the disadvantage of requiring ionising radiation, will not demonstrate strictures and gives no information on the condition of the affected gland. In addition it will not demonstrate radiolucent calculi, which account for 20-43 % of submandibular stones and more in the parotid. It is therefore necessary to supplement plain radiography with a sialographic examination.

Sialography is able to diagnose the presence and position of radiopaque and radiolucent salivary calculi, as well as strictures and the extent of ductal and glandular inflammatory destruction secondary to an obstruction. However this technique is painful, time consuming, technically demanding and requires ionizing radiation.

Ultrasound by comparison is a safe, simple and well-tolerated technique for the detection of salivary calculi and strictures. It is able to detect radiolucent stones even though the acoustic shadow is not as marked. Calculi detection rates vary between 63% and 94% and are equal to those for sialography. The distal portion of the submandibular and parotid ducts, require the use of intraoral probes.

In contrast to ultrasound, which depicts architecture, radioisotope imaging of the salivary glands gives some measure of the secretory function and allows comparison between the major glands. However, it exposes the patient to a relatively high radiation dose to the whole body. Miniature endoscopes allow direct visualisation of the ductal system and are increasingly used.

Treatment

Sialolithiasis

Approximately 40% of submandibular stones lie in the distal portion of the duct and can be removed by simple intra-oral procedures performed under local anaesthesia. However, for calculi that lie in the proximal duct or gland the treatment of choice has been sialadenectomy which is effective in eradicating symptoms but carries a moderate (3-7%) but real risk of nerve injury (facial, lingual and hypoglossal). Alternative, minimally invasive approaches include fluoroscopically guided basket retrieval, and lithotripsy. Using a combination of these techniques it is possible to render at least 70% of cases both stone free and symptom free. The selection criteria for these techniques are detailed in table 1. The principle that underpins this development is that the secretory function of the affected gland can regenerate after removal of the obstruction.

Strictures

Until recently the only treatment for symptomatic strictures was adenectomy. This carried with the attendant risks of neurological damage and cosmetic deformity, which are important considerations in the management of benign disease.

Balloon dilatation under fluoroscopic guidance and local anaesthesia is now being used although it is not always possible to negotiate the stricture (63%-90%). However in those where it was possible post-operative sialographic examination showed partial or total elimination of the stricture in 96% of cases with an associated improvement in symptoms.

Mucocoeles and salivary cysts

The mainstay of management for those affecting the lips or buccal mucosa is surgical removal under local anaesthesia. However, cryotherapy may provide a suitable alternative where there is a need or wish to avoid surgery.

In the case of a ranula a wide variety of treatments have been used with varying degrees of success. The key fact is that the sublingual gland must be removed if recurrence is to be avoided.

Prognosis and complications

Sialolithiasis and strictures

In the absence of intervention there is progressive reduction in salivary flow as a result of increasing obstruction often with superimposed infection. As a result, the gland progressively degenerates until it eventually ceases to function or presents with acute sialadenitis which requires sialoadenectomy.

Following glandular removal there is the risk of neurological deficit and the aesthetic complication of a facial scar. In comparison the morbidity associated with the newer techniques are minimal and relate primarily to post-operative infection and short-term discomfort. In addition in the case of strictures there is the possibility of it reforming which does not appear to be a significant problem in the case of salivary calculi.

Mucocoeles and salivary cysts

Those on the lips and buccal mucosa may resolve spontaneously or become chronic. In the case of the ranula it will persist until surgically removed as detailed above. The common complications of treatment are short-term discomfort and the risk of recurrence.

Prevention

Sialolithiasis

As there is no known aetiology there are no specific preventive measures.

Stricture/Mucocoeles

As with calculi, there are no specific preventive measures which the patient can undertake. However, it is important that the duct is handled with care during any surgical procedure. It should also be remembered that mucocoeles can occur as a complication of any lip biopsy.

Table 1

Submandibular calculus	Mobile	Any	Basket retrieval
	Fixed	Any	Intra-oral surgical release
Parotid calculus	Mobile	Any	Basket retrieval
	Fixed	Ostium	Surgical release
		Any	< 7 mm Lithotripsy
		Any	> 7 mm -Combined endoscopic/surgical

Further reading

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ORAL BIOPSY

Definition

There are oral lesions whose diagnosis can be made relying on data gathered during the history and/or physical examination, but there are others where histopathological studies are needed to confirm the presumed clinical diagnosis.
Biopsy is a surgical procedure to obtain tissue from a living organism for its microscopical examination, usually to perform a diagnosis

Objectives

The aim of the biopsy is to:

- define a lesion on the basis of its histopathological aspect;
- to establish a prognosis in malignant or premalignant lesions;
- facilitate the prescription of specific treatment;
- contribute to the assessment of the efficacy of the treatment;
- act as a document with medical-legal value.

Indications

Biopsy is indicated for diagnostic confirmation of suspected malignant lesions, precancerous lesions such as leukoplakias or erythroplakias and chronic ulcerations of unknown cause. It is also indicated for the histological confirmation of certain systemic disorders (Fig.1) and is recommended for apparently inflammatory lesions that do not improve within two weeks of removal of local irritants.
Other lesions that should also be biopsed include:

- lesions that interfere with oral function, such as fibrous hyperplasias and osseous lumps.
- lesions of unclear aetiology, particularly when associated with pain, paraesthesia or anaesthesia
- interstitial lesions in lingual, buccal or labial muscles
- radiolucent or radio-opaque osseous lesions.

When is oral biopsy not needed?

- There is no need to biopsy normal structures
- There is no need to biopsy irritative/traumatic lesions that respond to the removal of a presumed local irritant

- There is no need to biopsy inflammatory or infectious lesions that respond to specific local treatments, as pericoronitis, gingivitis or periodontal abscesses
- No incisional biopsies should be performed on suspected angiomatous lesions.

Types of biopsy

According to the procedures applied, oral biopsies can be classified by:

a) Features of the lesion:
   - direct biopsy: when the lesion is located on the oral mucosa and can be easily accessed with a scalpel from the mucosal surface.
   - indirect biopsy: when the lesion is covered by an apparently normal oral mucosa

b) Area of surgical removal:
   - incisional biopsy: consists of the removal of a representative sample of the lesion and normal adjacent tissue in order to make a definitive diagnosis before treatment.
   - excisional biopsy: is aimed at the complete surgical removal of the lesion for diagnostic and therapeutic purposes. This procedure is elective when the size and location of the lesion allows for a complete removal of the lesion and a wide margin of surrounding healthy tissue (Fig.2).

c) By the timing of the biopsy:
   - Pre-operative
   - Intra-operative
   - Post-operative when aimed at checking the efficiency of a treatment.

General principles of oral biopsy:

Before the procedure is undertaken, the characteristics of the lesion (size, shape, colour, texture, consistency, time of evolution, associated signs and symptoms, regional nodes) should be described in the patient's clinical records together with a presumed diagnosis and possible differential diagnosis.

The patient should receive information on the technique that will be performed and the reasons why it is performed, avoiding terms that may cause anxiety. Informed consent is required.

Regarding the surgical technique:

- Regional block local analgesia rather than infiltrative techniques is preferred;
- elliptical incisions should be attempted in order to ease suture;
- incisions parallel to nerves and vases are preferred;

- if the lesion is smaller than 1 cm, excisional biopsy should be performed. If larger, an incisional technique including representative areas of the lesion with healthy margins should be chosen;
- when a malignant lesion is suspected, incisional technique is mandatory.

Samples must be oriented with a suture or a piece of paper, and introduced in a container with a fixing solution (10% formalin) (Fig.3)

The number and location of the biopsies will be decided on the basis of the clinical appearance of the lesion. If a lesion shows several areas where biopsy would be indicated, more than one sample should be taken. In these cases with precancerous or suspicious lesions, toluidine blue staining could be useful to choose the areas most relevant to biopsy.

The biopsy should be large enough to include normal and suspicious tissue and for the pathologist to give a diagnosis without further specimens (small samples are difficult to orientate and handle and certain processes as sample fixation may end in a reduction of the size of the specimen).

There are different procedures for undertaking oral biopsies. However, the selection of both technique and surgical instruments to use to avoid artefacts is controversial. The use of CO_2 laser for the procurement of diagnostic biopsy specimens is compromised by thermal cytological artefacts. Problems of this nature are also witnessed with electrocautery. Punch biopsy has been suggested to reduce artefacts (Fig.4), although this has not been confirmed under controlled experimental conditions. Punch biopsy may tear the tissue in vesiculobullous conditions. Scalpel biopsy is the most widely accepted technique and the one that shows fewer limitations for obtaining samples from the oral cavity.

Scalpel technique for biopsy taking:

In order to obtain good visibility, good illumination is needed. A Farabeuf-type separator or similar instrument to retract the lips and cheeks, and moderate-volume surgical aspiration are required.

The instruments suggested are:

- Cartridge-type local anaesthetic syringe
- Fine, single use, two-sided needles
- Cartridges of local anaesthetic solution
- Small and short scalpel blades (no. 15, 11, 12 or even 5)
- Mosquito forceps
- Allis tweezers
- 2/0 to 5/0 non-traumatic suture material

- Gauze
- Container with fixing solution

A biopsy technique can be reduced to six steps: selection of the area to biopsy, preparation of the surgical field, local anaesthesia, incision, handling of the specimen and suture of the resulting wound.

1. Selection of the area to biopsy

When dealing with small-sized lesion, an excisional biopsy will be performed, whereas incisional biopsy performed in the most representative area of the lesion is used for large lesions (long axis larger than 1 cm). If there is any doubt about the malignant character of the lesion, vital staining with toluidine blue can be use as an adjunct to select representative areas (Fig.5). Toluidine blue is a basic dye that fixes to nucleic acids and stains the nuclear content of malignant cells; in these cases samples should be taken from areas with deep blue patches, as light blue areas are not significant. Toluidine blue is used in three steps:

- wash the area with 1% acetic acid
- apply a 1% toluidine blue water solution for 1 minute
- mouthwash with 1% acetic acid

The sample must include healthy tissue at the margin of the lesion.

2. Preparation of the surgical field.

The surgical area is disinfected with a quaternary ammonium compound. Iodine-containing surface antiseptics should not be used, as they may stain the tissues. A 0.12- 0.20 % chlorhexidine solution is preferred.

3. Local anaesthesia:

An amide-type local anaesthetic with vasoconstrictor should be used and infiltrated away from the lesion are to avoid introducing artefacts in the sample.

4. The incision:

Oral tissues should be immobilized far from the area to biopsy with non-toothed tweezers. A clean and defined incision is performed to obtain a slice of tissue when aiming at incisional biopsy. Soft tissues incisions should be elliptical in shape producing a “V” wedge that includes both the lesion and healthy margins. If various lesions are present, multiple biopsies should be taken.

5. Tissue handling

The specimen is handled gently to avoid crush artefacts and introduced in the fixing solution. The role of the fixing agent is to preserve the cellular architecture of the tissues. There are authors that suggest the placement of the specimen on a sterile paper with the mucous surface facing upwards to avoid distortion and curling of the sample margins.

The best fixing agent is a 10% formalin solution, as it induces less ultrastructural alterations in the samples. 70% ethanol can also be used. The samples should never be put in isopropyl or methyl alcohol, saline or distilled water - as severe alterations may be provoked.

The volume of the fixing agent should exceed 10 to 20-fold the volume of the sample.

When immunofluorescence or immunostaining are needed, specimens should not be fixed, but sent as soon as possible to the laboratory for freezing or put in Michel's solution.

When the material is sent to the pathologist, it should be accompanied with a detailed report that includes identification of the patient, clinical records, clinical signs and a probable diagnosis as well as the orientation of the sample. An explanatory diagram of the biopsy area may be useful for this purpose.

6. Suture

The suture should achieve good haemostasis, facilitate healing and should be removed after 6-8 days

What are the most frequent errors that should be avoided when taking oral biopsies?

In order to obtain a quality, artefact-free oral biopsy that permits the pathologist establish a histological diagnosis, the clinician should avoid:

- pressing the sample with the tweezers, particularly if toothed, as may produce tissue tears and "pseudomicrocysts"
- infiltrating anaesthetic solution within the lesion, as it can cause sample alterations
- applying products to the lesion that induce tissue modifications
- using an insufficient volume of fixing solution
- inclusion of undesired material in the sample: glove powder, calculus, restorative materials, etc.
- taking insufficient amount of tissue in extension and depth.

Pictures:

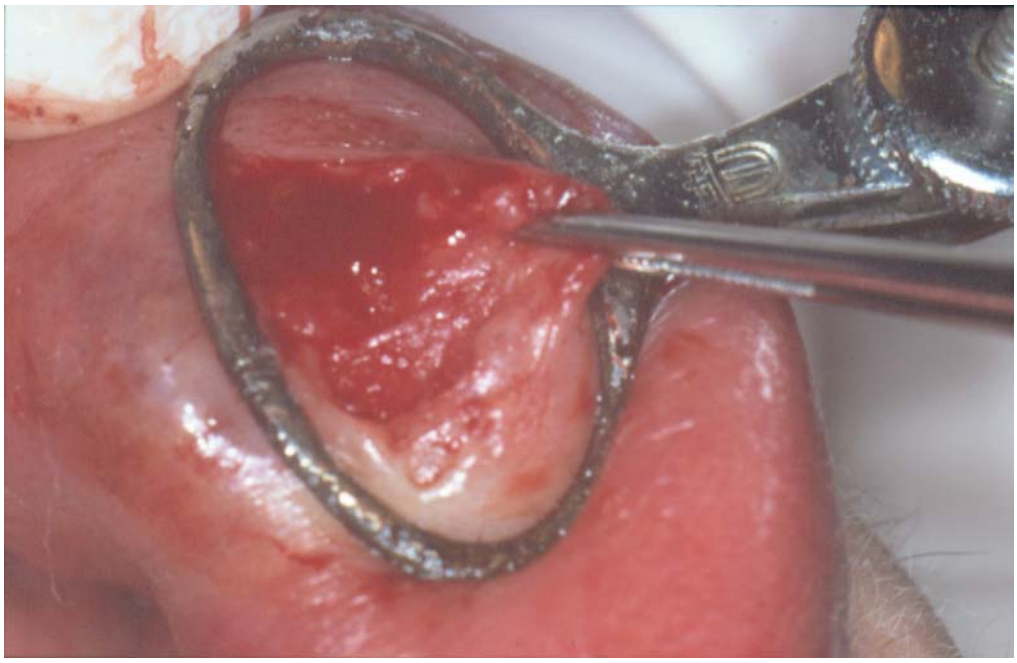

Figure 1. Biopsy of minor salivary glands for diagnosis of Sjögren syndrome.

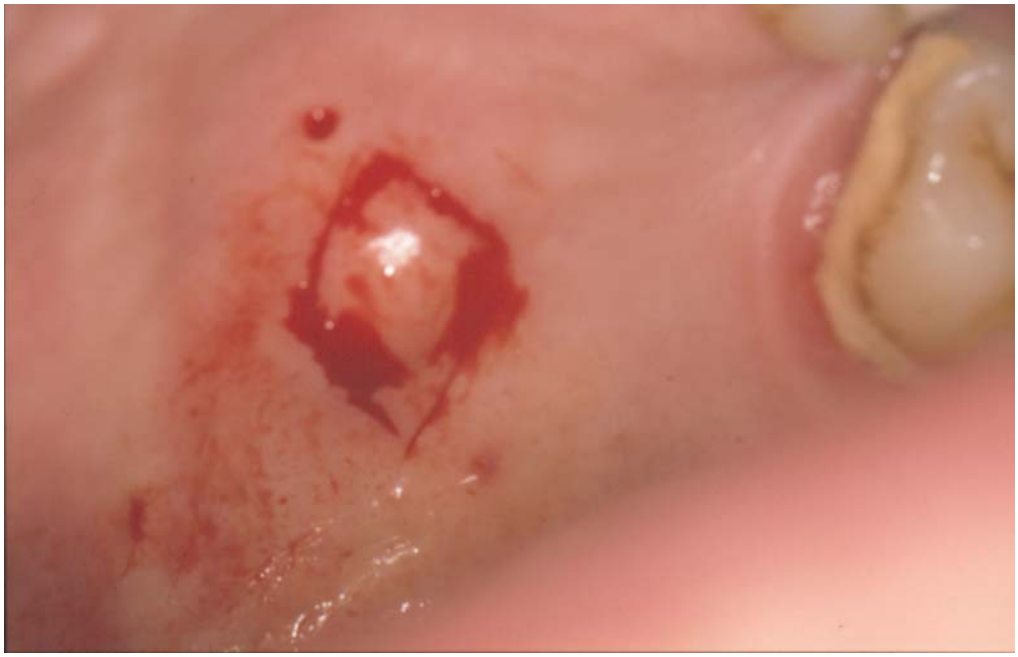

Figure 2. Excisional biopsy of a nodular lesion of the palate.

Figure 3. Container with a fixing solution.

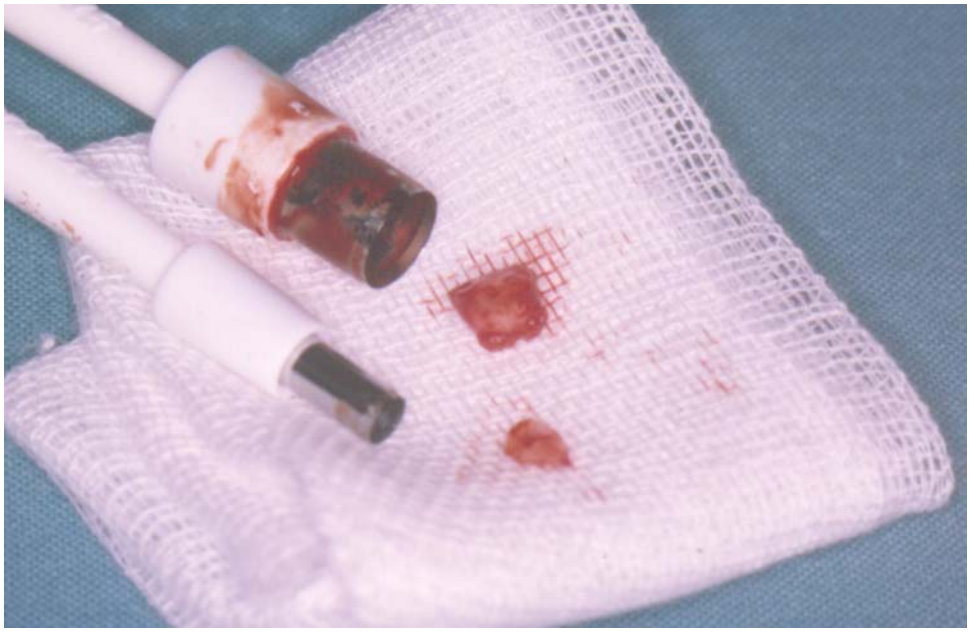

Figure 4. Specimens obtained by punch biopsy.

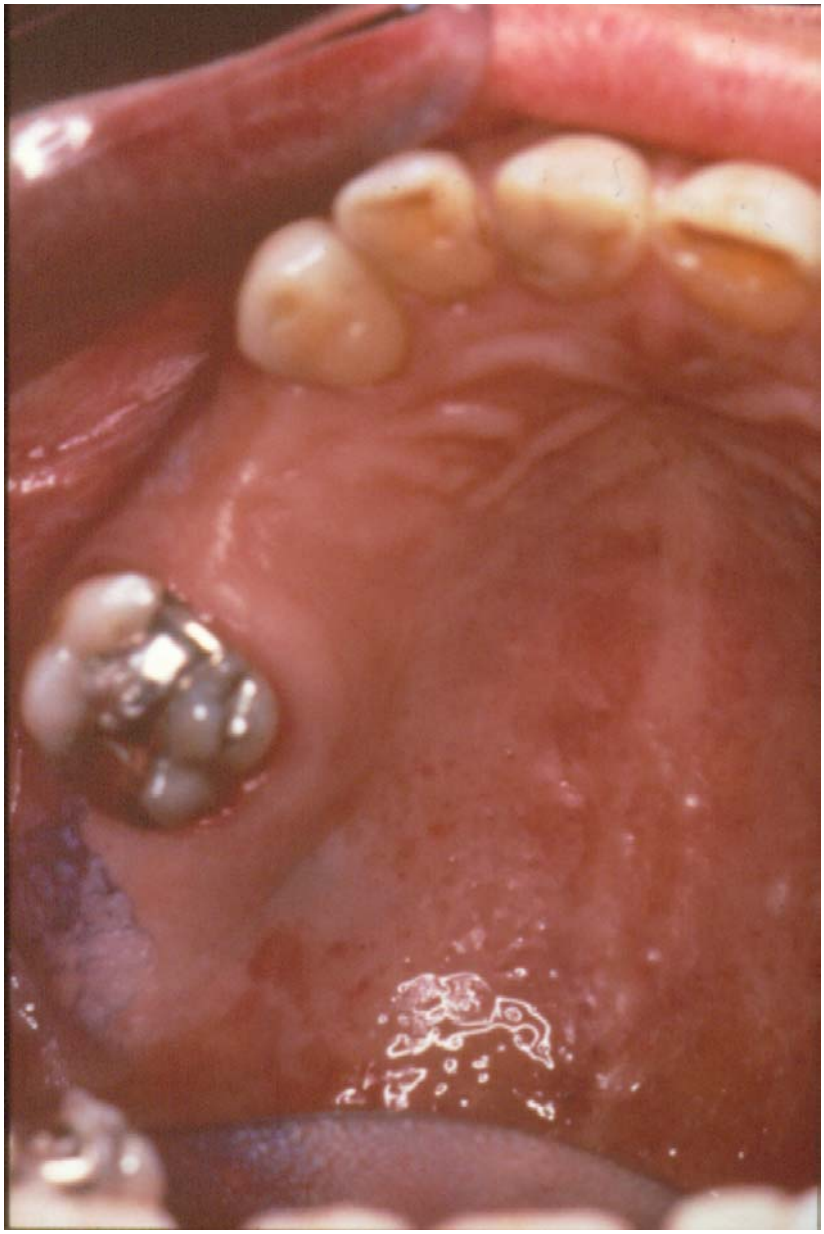

Figure 5. Toluidine blue is used to select the representative areas.

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Links

http://www.eastman.ucl.ac.uk/~eaom/clinical_support.html

ORAL CANCER

Definition

About 2% of all malignancies that can occur in the body arise in the oral cavity. In some areas of the world this percentage is higher. The majority of malignancies consist of squamous cell carcinomas of the covering oral mucosa, while the remaining include malignant tumours of salivary gland, lymphoreticular disorders, bone tumours, malignant melanomas, sarcomas, malignant odontogenic tumours, and metastases from tumours elsewhere in the body.

Epidemiology

The incidence of squamous cell carcinomas of the oral cavity differs widely in various parts of the world and ranges from approximately 2 to 10 per 100,000 population per year. Such differences can to some extent be explained on the basis of environmental differences or life-style and habits among certain populations, such as betel-quid chewing, snuff dipping or the habit of reverse smoking. High incidence countries include those in south Asia such as Sri Lanka, India, Pakistan and Bangladesh; Bhas Rhin and Calvados regions in France; countries in central and eastern Europe; and Brazil. The incidence of oral carcinoma in Blacks is somewhat lower than in Whites, which is mainly due to the lower incidence of lower lip cancer in Blacks.

In most parts of the world the male-female ratio is approximately 2:1 for oral carcinomas, except for carcinomas of the vermilion border of the lower lip. In the latter site there is a strong male predominance. Oral squamous cell carcinomas are mainly found after the fourth decade.

Aetiology

Use of tobacco in its various forms, including the use of smokeless tobacco, is regarded to be the main cause of oral cancer, particular when associated with the use of excess alcohol. High exposure to ultraviolet light increases the chance of developing cancer of the lower lip. Diets with low levels of vitamins A and C or inadequate consumption of vegetables and fruits may contribute to the risk of oral cancer.

Patients who are immunosuppressed, e.g. renal and homograft recipients and HIV-infected patients have a higher incidence of subsequent cancer development, particularly of the lower lip. Furthermore, a number of rare conditions predispose to the development of oral cancer, such as xeroderma pigmentosum, Fanconi's anaemia, and Bloom's syndrome.

In some patients with oral cancer, especially in females, none of the aforementioned factors or cofactors seem to be present, which makes the development of oral cancer all but completely understood.

Oral epithelial carcinogenesis seems to be a multistep process, also referred to as clonal evolution, that may be interrupted at various points. It has not been possible yet to identify chromosomal

regions containing specific genes that may play a specific role in the development of squamous cell carcinoma of the head and neck, but existence of allelic imbalance in gene loci at chromosomes 3p and 9p have been reported. Three sorts of genes have been implicated in the genesis of cancer: proto-oncogenes, that display dominant, gain of function mutations in cancer cells; tumour-suppressor genes, which are affected by recessive, loss of function mutations; aberrations in DNA repair genes. For a detailed account of molecular pathogenesis of oral cancer check references.

Clinical aspects

The primary

In European populations many oral cancers may arise *de novo*. In a high proportion of cases, however, oral cancer is preceded by clinically visible whitish (leukoplakia) or reddish (erythroplakia) changes in the oral mucosa. The most common locations of oral squamous cell carcinomas are the borders of the tongue, the floor of the mouth, and the vermilion border of the lower lip. In tobacco or betel quid chewers buccal grove and retromolar mucosa may be involved . A small percentage of patients with oral cancer have multiple primary squamous cell carcinomas, either elsewhere in the oral cavity or in the upper aero-digestive tract.

The average duration of symptoms is usually around four to five months, ranging from a few weeks up to one year. Part of the delay in diagnosis is due to the patient's lack of awareness of a serious condition ("Patient's delay") and as cancer in the mouth is not thought of as a likely event. Relatively small carcinomas, measuring less than 1 cm, may be asymptomatic, being discovered as an incidental finding during routine dental examination. Patients with larger tumours may have varying complaints. In carcinomas of the tongue, pain is often the first symptom; this may be localised to the tongue or referred (e.g. to the ear). Some patients have noticed an ulcer or a growth of their oral mucous membrane, or just a whitish or reddish change that urges them to seek medical advice. Few patients with oral cancer will seek medical help because of an enlarged node in the neck as the first symptom.

Asymptomatic squamous cell carcinomas often show erythroplastic changes, either smooth or granular in texture, without induration. In symptomatic tumours, usually measuring more than 1 to 2 cm, the most frequently encountered feature is an indurated area of ulceration. A squamous cell carcinoma may also manifest itself as an exophytic, papillary, or as a verrucous growth without much invasiveness, also referred to as verrucous carcinoma.

Regional metastases; distant metastases

Attention must be paid to the potential spread of oral cancers to the cervical lymph nodes. In midline or near-midline cancers, contralateral and bilateral lymphatic spread may occur. The chance of lymphatic spread is mainly influenced by the site and size of the primary. Evidence of distant metastases of oral cancer at the time of admission is rare, but is seen frequently in late

stages of the disease.

Diagnosis

The suspicion of malignancy is in most cases based on the clinical findings. The most significant feature noted in malignant disease is the presence of induration on palpating the margins or base of the lesion. The application of toluidine blue staining can be a useful additional tool in the diagnostic procedure of oral carcinoma. Exfoliative cytology and the more recently introduced brush biopsy assisted by computerised detection of abnormal cells can be other helpful diagnostic tools. It is, nevertheless, recognised that neither toluidine blue staining nor brush biopsy is a substitute for an adequate scalpel biopsy that allows for histopathologic examination.

The UICC (Union Internationale Contre Cancer) has developed a TNM (Tumour, Node, Metastasis) classification for 28 sites in the body, including the oral cavity (Table I) to grade the size and extent of tumour spread. New imaging techniques are also employed to assist the clinician in assessment of spread of disease. Examination under general anaesthesia is recommended to survey the upper respiratory and alimentary track for possible second primaries or precursor lesions.

Treatment, and follow-up

Dental and oral care

Dental caries and periodontal diseases have to be taken care of adequately before therapy, whether surgical or radiological, is instituted. Root remnants and impacted teeth should be removed as well, especially when radiotherapy is anticipated in the course of treatment as this will minimize the future risk of osteoradionecrosis of the jaw bones. If extractions or surgical removal of teeth are indeed necessary, a time interval of one to two weeks should be allowed before commencement of treatment by radiotherapy. In the presence of an ulcerative oral malignancy, extraction or surgical removal of teeth is a debatable procedure because of the risk of contamination of the wound with tumour cells.

When radiotherapy will be instituted, regular application of topical fluorides is strongly recommended for the protection of the teeth, not only during but also after radiotherapy, since irradiation damages the salivary glands. The resulting hyposalivation strongly predisposes to the development of (radiation) caries and, to a lesser degree, of periodontal disease. Furthermore, hyposalivation causes a very uncomfortable feeling of oral dryness (xerostomia). Apart from frequent mouth rinses and the use of artificial saliva, the use of parasympathomimetic drugs such as pilocarpine hydrochloride may be considered in the management of xerostomia.

In patients who have undergone irradiation of the head and neck region, and in which the jaw bones have been included in the field of irradiation, antibiotic prophylaxis is required for every tooth extraction, even when simple and undertaken many years after the irradiation, in order to avoid the

development of the severe form of osteomyelitis of the jaw bone, called osteoradionecrosis.

Surgery

Most head-and-neck oncology centres prefer primary surgery and, in selected cases, postoperative radiation rather than preoperative radiation and then surgery. In general, the aim is to obtain a margin of at least one centimeter of clinically healthy tissue when excising a squamous cell carcinoma.

In the presence of lymph node metastases, a neck dissection may be carried out at the same time, either in continuity with the primary tumour ("en bloc" procedure) or as a separate, delayed procedure. For a number of reasons a prophylactic or elective neck dissection may be indicated in the absence of clinically detectable lymph node metastases. It is beyond the scope of this chapter to discuss in detail the various modifications in neck dissections.

Radiotherapy

In several centres radiotherapy is given as the treatment of first choice, particularly in T1 and T2 oral squamous cell carcinomas, including those of the lower lip. The total dose is in the range of 60-70 Gy, given in multiple fractions, usually as 2 Gy per day. Dose fractionization regimes have been widely researched in many centres and can significantly improve the prognosis. After radical radiation, surgery may still be effective in case of residual or recurrent tumour growth ("Salvage surgery").

Preoperative radiotherapy is also sometimes used. In advanced squamous cell carcinomas preoperative chemo-radiotherapy may be administered. Radiotherapy is often applied postoperatively if the surgical margins have not been cleared, or because of the presence of multiple cervical lymph nodes, or when one or more lymph nodes show extracapsular spread.

Chemotherapy

In general, chemotherapy is not currently being used as the treatment of first choice in oral squamous cell carcinoma. However, it may be useful in advanced oral cancer as a preoperative or preradiotherapeutic modality.

Habit intervention

In all cases where there is a known risk habit suitable support must be provided to quit tobacco and to moderate alcohol use. Overall prognosis of patients continuing these habits is reportedly poor.

Prognosis

The prognosis for a patient with oral carcinoma depends largely on the size, tumour thickness, pattern of invasion, perineural invasion, and site of the primary tumour as well as on the presence or absence of metastatic spread (Table II).

One should realize that survival figures are based on large series of patients and are of limited value for the individual patient. Indeed, some patients with large oral cancers do better than

expected, while others with very small oral cancers may do worse. There is clearly a biological variation of the tumour as well as the oral cancer patient that is not fully understood.
The cause of death in patients with squamous cell carcinoma of the head and neck is mainly due to recurrent locoregional disease and to a lesser extent to distant metastases.
Many patients with oral cancer have chronic heart, lung, and liver diseases and other problems related to alcohol ingestion or smoking; this co-morbidity is estimated to account for 30 per cent of deaths among patients with oral cancer.
Patients who have been treated for oral cancer are at risk of getting a second primary tumour either in the head and neck region or elsewhere in the body. Therefore, long term follow-up programmes including panendoscopy are important.

Prevention and screening

Primary prevention of oral cancer mainly focuses on avoidance of the use of tobacco, alcohol and betel quid (areca nut). Secondary prevention is aimed at the early recognition of oral cancer, while tertiary prevention refers to the prevention of new cancer development after treatment of cancer.
Dentists and physicians can play a major part in preventing oral precancer and cancer by encouraging a healthy lifestyle, particularly with regard to quitting tobacco use and moderating alcohol consumption. Intake of 5 or 6 portions of fresh fruit and vegetables per day is recommended. Case evaluation should always include questions about numbers of cigarettes smoked each day (or other tobacco usage) and units of alcohol consumed per week. One of the problems encountered in programmes of behaviour modification is the distorted public perception of risk where rare risk factors are often given greater emphasis than the more important dangers such as alcohol and tobacco use.
Screening programmes are recommended for the detection of oral cancer in high-risk populations of the Third World and in high risk group patients in Western countries. Inspection of the oral cavity should also be part of every physical examination in the physician's and dentist's offices, particularly in patients older than 50 years who are heavy users of tobacco and alcohol. Optimal frequency for screening for oral cancer has not yet been determined but annual screening allows detection of new lesions.

Table 1. UICC TNM classification of malignant tumours (UICC, 2002)

T Primary Tumour			
TX	Primary tumour cannot be assessed		
T0	No evidence of primary tumour		
Tis	Carcinoma in situ		
T1	Tumour 2 cm or less in greatest dimension		
T2	Tumour more than 2 cm but not more than 4 cm in greatest dimension		
T3	Tumour more than 4 cm in greatest dimension		
T4a	*(lip)* Tumour invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin (chin or nose)		
	(oral cavity) Tumour invades through cortical bone, into deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, or skin of face		
T4b	*(lip and oral cavity)* Tumour invades masticator space, pterygoid plates, or skull base, or encases internal carotid artery		
N Regional Lymph Nodes			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension		
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension		
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension		
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension		
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension		
N3	Metastasis in a lymph node more than 6 cm in greatest dimension		
M Distant Metastasis			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Stage grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1, T2	N1	M0
	T3	N0, N1	M0
Stage IVA	T1, T2, T3	N2	M0
	T4a	NO, N1, N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Note: Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumour as T4.

Table 2. 5-year survival in oral cancer

Subsite	**Overall**	**According** to stage			
		I	II	III	IV
Mobile tongue	45%	80%	60%	30%	15%
Floor of mouth	50%	80%	70%	60%	30%
Buccal mucosa	45%	75%	65%	30%	15%
Retromolar trigone	60%	75%	70%	60%	30%
Lower gingiva	65%	75%	60%	50%	60%
Lip	85%	90%	85%	70%	60%

Ph. Rubin. Clinical oncology. A multidisciplinary approach for physicians and students. 7th edition, 1993. W.B. Saunders Company, Philadelphia London Toronto Montreal Sydney Tokyo. ISBN 0-7216-3761-2

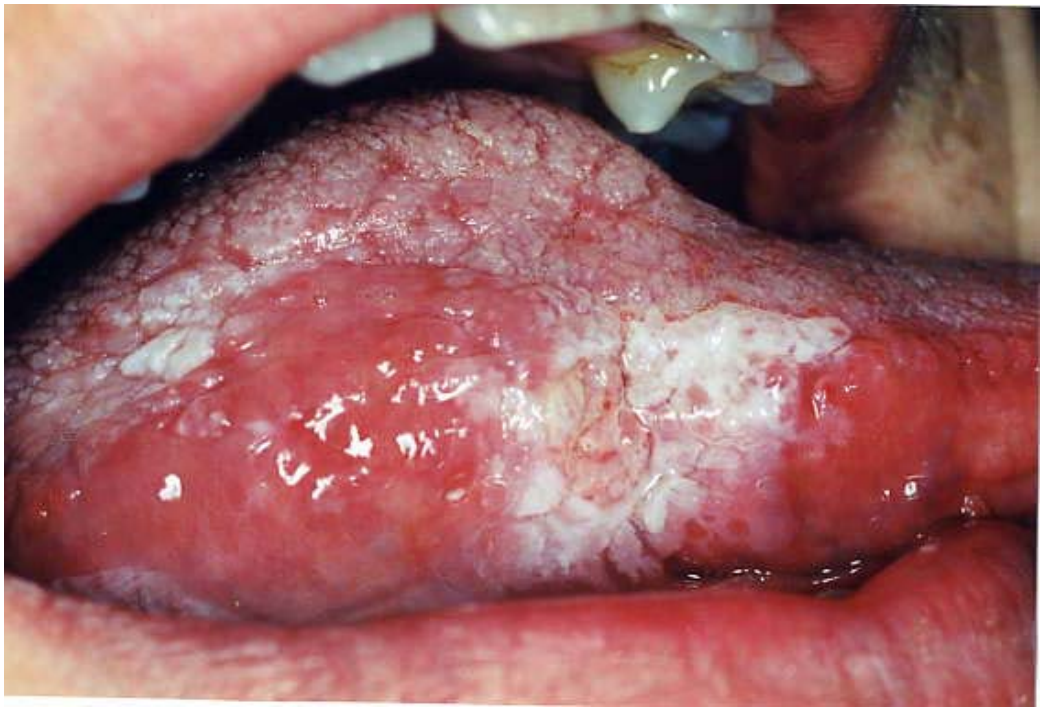

Figure 1. Ulcerative lesion of lateral tongue with a keratotic border raising the suspicion of a carcinoma in a young adult male smoker

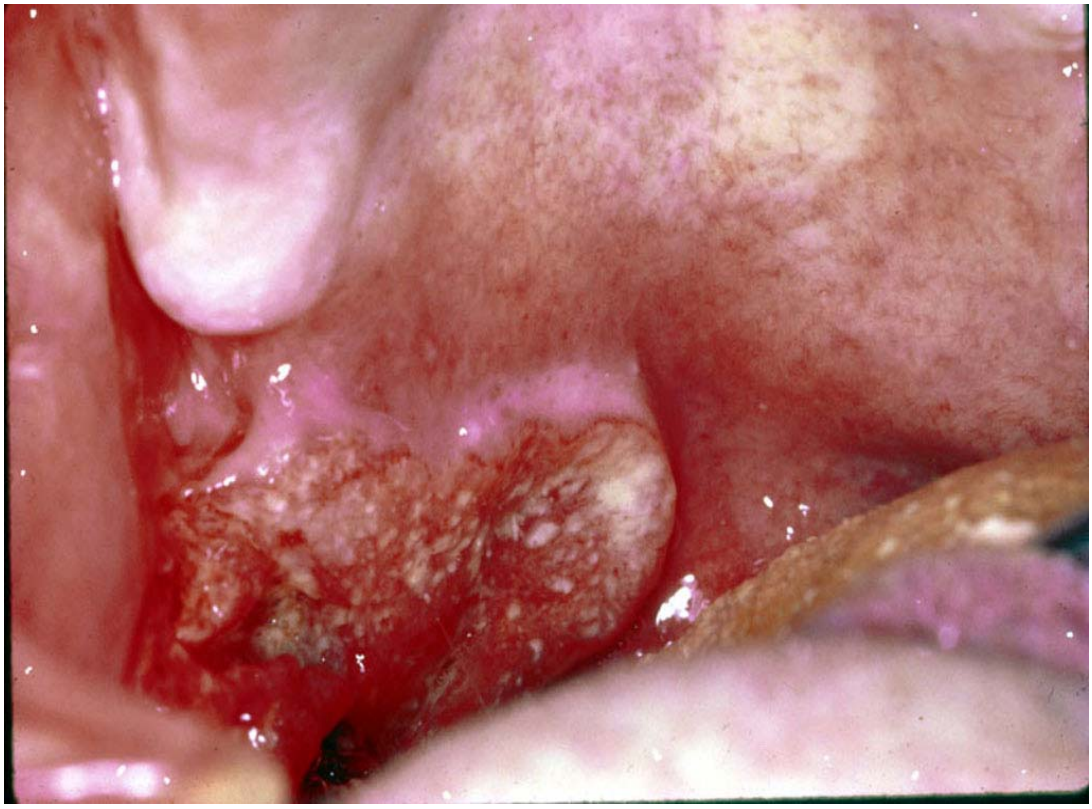

Figure 2. A non-healing ulcer of soft palate extending to oro-pharynx in an elderly male

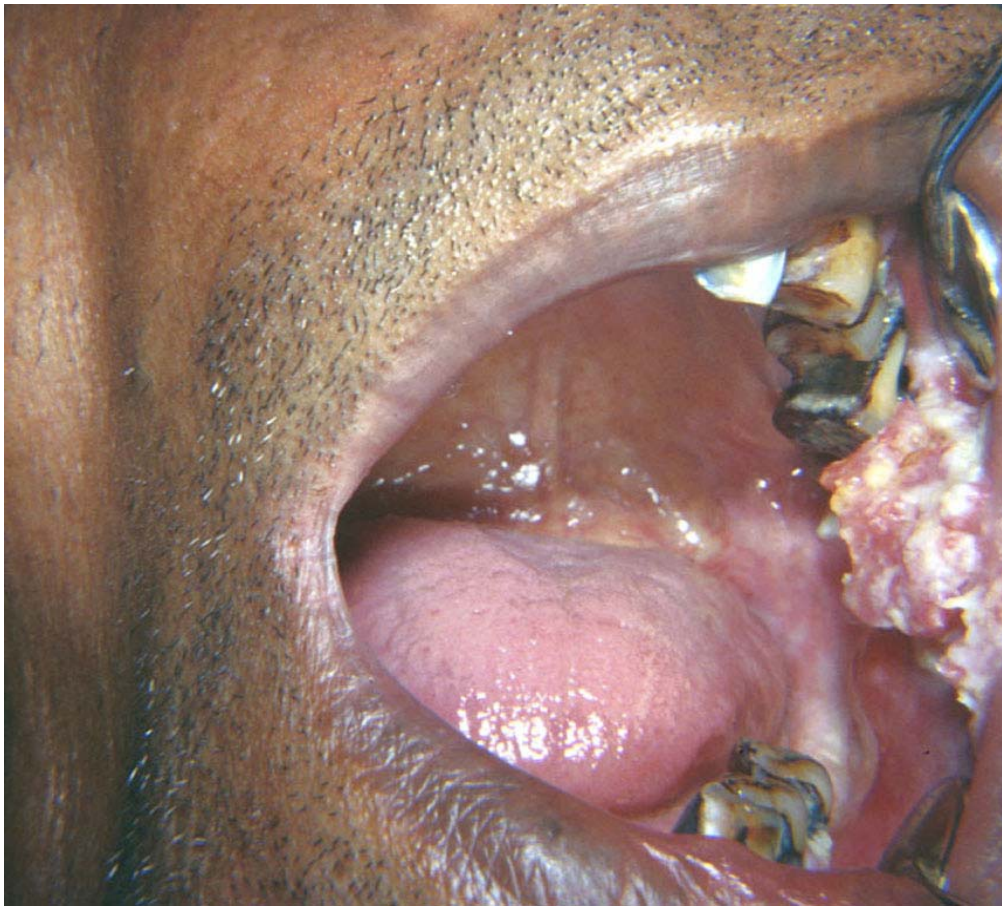

Figure 3. A verrucous carcinoma of commisure and cheek in an Asian areca/betel quid chewer

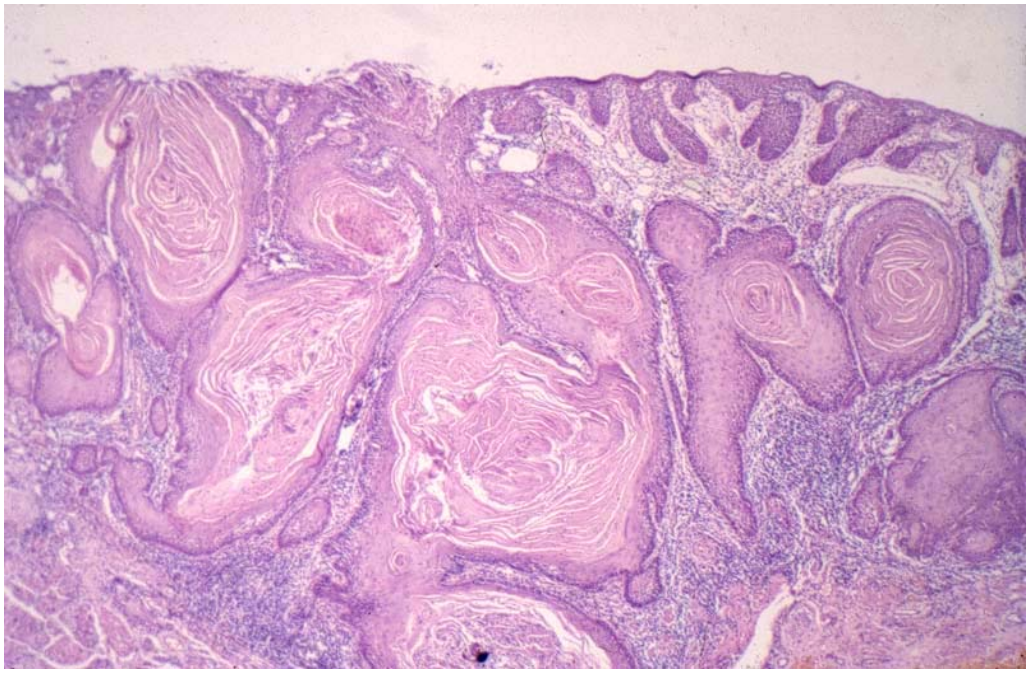

Figure 4. Well-differentiated squamous cell carcinoma of the oral mucosa

Further reading

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ORAL CANDIDOSIS

Definition

Oral candidosis and oral candidiasis are synonymous.

Oral candidosis is the most common oral fungal infection in man and it is caused by different *Candida* species, usually *C.albicans*.

Candida is a yeast, which is an obligate organism in humans and a normal constituent of the digestive and vaginal tracts.

Candida species are opportunistic pathogens, which may cause disease mostly when there are changes in oral ecology or when the host defenses have been compromised, hence the epithet “candidosis is the disease of the diseased”.

Oral candidosis, in the form of thrush (whitish, semi-adherent membranes), has been known since ancient times (Hippocrates, 600BC), as a disease mostly affecting infants and debilitated individuals. During the last three decades, candidosis reemerged as an important disease with the introduction of broad-spectrum antibiotics, organ and bone marrow transplantation, immunosuppressive therapies, and the pandemic of human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS). Oral candidosis is the earliest and most common manifestation of HIV-infection.

Epidemiology

Candida species reside in the oral cavities of a majority of healthy individuals as commensal organisms, with a colonization prevalence ranging between 30% to 40%. Oral *Candida* carriage increases, up to 75%, in immunocompromised and immunosuppressed individuals, in HIV-infected patients, in patients receiving anticancer chemotherapy and in head and neck cancer patients receiving radiotherapy.

Candida albicans accounts for 70% to 95% of the oral isolates, from smears taken from either healthy individuals or from lesions of clinical infection. *Candida tropicalis*, *Candida krusei*, *Candida glabrata*, *Candida parapsilosis*, *Candida guilliermondii*, *Candida famata* and *Candida dubliniensis* are less commonly isolated species. An epidemiological shift of *Candida*, with a change from single to multiple *Candida* species isolates has recently been reported in several groups of patients, with an incidence ranging from 7% to 29%.

The dorsum of the tongue is the primary oral reservoir, which may, at least partially, explain why the dorsum of the tongue is a major location of different forms of oral candidosis.

In HIV subjects, oral candidosis is the most frequent HIV-related oral lesion, affecting about half of the HIV-infected patients who do not receive antiretroviral therapy.
In head and neck cancer patients treated with radiotherapy, oral candidosis will develop in at least one out of three patients.

Clinical presentation

Oral candidosis may present with a variety of clinical patterns or forms. We can consider: acute forms (erythematous, pseudomembranous), chronic forms (erythematous, pseudomembranous, hyperplastic), candida-associated lesions (angular cheilitis, denture-related stomatitis, median rhomboid glossitis), and oral manifestations of systemic mucocutaneous candidosis.
Some patients may exhibit more than one clinical form of candidosis and in more than one oral site, thus presenting with multifocal candidosis. Oral candidosis is, in most cases, endogenous and most often remain superficial and localized in the oral mucosa. Regional extension and systemic or deep-seated candidosis may occur, but it is relatively uncommon.
Erythematous candidosis *(atrophic)* is the most common type. Before the era of AIDS, it was most commonly seen after the use of antibiotics. This acute painful lesion is characterized by a diffuse loss of the filiform papillae of the dorsum of the tongue, which appears red (Figure 1). Erythematous candidosis in HIV disease appears as asymptomatic red areas or patches usually located on the dorsum of the tongue and the hard palate (Figure 2). The patient may seek consultation because of dysgeusia or xerostomia.
Pseudomembranous candidosis (*thrush*) appears as semi-adherent, whitish or yellowish, soft, drop-like or confluent membranes or plaques, which resemble curdled milk (Figure 3). These pseudomembranes can be wiped off, and reveal a red underlying mucosa. Any mucosal surface may be affected. The pseudomembranes consist, mainly, of tangled masses of candidal pseudohyphae, with budding yeast cells (Figure 4), desquamated epithelial cells, and debris. Patient may complain of a burning sensation, xerostomia, dysgeusia or anorexia (loss of appetite). Pseudomembranous candidosis is rarely painful.
Angular cheilitis (*perleche*) of candidal aetiology presents as red fissures radiating from the commissures of the mouth, sometimes covered by dry, crusting membranes (Figure 5). The scaling and fissuring may extend on the vermilion border, thus, presenting similar to exfoliative cheilitis. Angular cheilitis in general, is bilateral, and may develop alone or with other forms of candidosis.

Chronic hyperplastic candidosis is a rare form of candidosis presenting as white plaque, infiltrated by *Candida* hyphae. This lesion should heal after antifungal treatment. Oral hyperplastic candidosis may also be seen in association with immunologic or endocrine abnormalities.
Some cases of median rhomboid glossitis, denture stomatitis and linear gingival erythema may be associated with candidal infection. These cases will respond and heal after antifungal treatment.
Several other oral mucosal diseases, such as lichen planus, may be secondarily infected by *Candida* organisms, increasing the severity of the disease.
Candida may, also, secondarily infect cases of oral leukoplakia, increasing the risk for malignant change.

Aetiopathogenesis

As the term “candidosis” implies, the cause of the disease, is the yeast *Candida*. *Candida* species may cause an “opportunistic” infection, under certain predisposing host factors. Local and systemic host factors often co-exist and act in a synergistic fashion.
Virulent yeast-related factors play a role in the development of disease, too.
Local host factors

- Loss of integrity of the oral mucosa.
- Thin or ulcerated epithelium, resulting from an ill-fitting denture, or after anticancer chemotherapy or head and neck radiotherapy, ect., allows for *Candida* to adhere on the epithelial cells, penetrate the mucosa, and cause infection.
- Heavy smoking, non-specific leukoplakia and other oral mucosal diseases make oral mucosa prone to the development of candidal infections.
- Xerostomia result in decreased flushing action and in reduced antifungal components of saliva, thus enhancing the development of candidosis.
- Local corticosteroids, via local immunosuppression, also promote oral candidosis.

Systemic host factors

- Immunodeficiency and immunosuppression are important host factors, especially in view of the increasing numbers of patients with acquired immune deficiency syndrome/AIDS and of individuals who receive corticosteroid or immunosuppressive or cytotoxic treatment (organ and bone marrow

transplant recipients, patients with malignant disease, patients with autoimmune disorders).

- Broad spectrum antibiotics may enhance the development of candidosis mainly by locally disturbing oral ecology.
- Dietary factors, such as poor nutrition, iron and vitamin deficiencies locally alter the integrity of the oral mucosa, promoting the development of candidosis.
- Endocrine disorders, such as diabetes mellitus, haematologic dyscrasias, malignant diseases, age (neonatal, elderly) also enhance candidosis.

Diagnosis

A presumptive diagnosis can be made on the basis of the different clinical forms of candidosis. Thus, a good knowledge of the clinical forms of the infection is the first important step.

The definitive diagnosis of candidosis is established by the clinical signs, in conjunction with positive direct microscopic findings or culture, while positive response of the lesion to antifungal therapy, which is the principal defining criterion, is necessary to confirm the diagnosis. No definitive colony count has been established that allows for differentiation between commensalisms and disease. Therefore, a positive culture in the absence of signs and symptoms does not necessarily imply candidal disease.

The differential diagnosis, in the case of erythematous candidosis, will mainly include the geographic tongue and atrophy/erythema due to iron or B_{12} deficiency anemias. In the case of candidosis during chemo- and/or radio- therapy, the infection has to be differentiated from chemo- and radiation-induced mucositis. Again, healing of the lesion following antifungal treatment is the principal differentiating/defining criterion.

Candida organisms penetrate the epithelium, causing inflammation, with oedema and polymorphonuclear leukocyte aggregation (microabscess formation). Hence, exfoliative cytologic examination or smear taken by rubbing a sterile cotton swab over the lesion will reveal, upon direct microscopic observation, *Candida* hyphae, blastospores, epithelial cells, and polymorphonuclear leukocytes. Hyphae and blastospores may be demonstrated with potassium hydroxide, periodic acid Schiff or Gram's stain.

Apart from smear and cytology, several other laboratory techniques may be also used such as imprint culture, impression culture, salivary culture, oral rinse technique.

Culture of the clinical material will define the pathogenic *Candida* species. The identification of the different *Candida* species depends on a combination of morphological and physiological characteristics.
The serodiagnosis of *Candida* infection is important in systemic candidosis.

Treatment

The management of patients with oral candidosis involves the identification and elimination of predisposing factors, as discussed above (see pathogenesis), and the use of antifungal medications. If the predisposing factor can not be eliminated or treated, candidosis is likely to recur.
At present, the aim of antifungal treatment is the healing of the clinical infection. The time required to achieve healing of the clinical infection is usually one to two weeks. Eradication of the yeast (mycological cure) from the oral cavity of a carrier is difficult to achieve or it may not be possible, as in AIDS patients or in head and neck cancer patients after radiotherapy. Even after total eradication of the yeast from the oral cavity, recolonization from the gastrointestinal tract or the vagina may occur.
Several antifungal agents are available for topical or systemic use, depending on the form and the extent of the infection, the *Candida* species isolated and, most importantly, the condition of the host and the underlying pathology.
Nystatin (formulated as suspension and pastille) was the first effective antifungal drug, for topical use. It is not absorbed across the gastrointestinal tract. Due to its sucrose content, it is not indicated in xerostomia-related, caries-prone individuals.
Amphotericin B (as suspension and lozenge), clotrimazole (as troche), and miconazole (as gel) are also useful for topical treatment. Miconazole is also effective against staphylococcal infections, hence, miconazole oral gel is best for the treatment of angular cheilitis.
Ketoconazole (as tablets) due to its potential liver toxicity, is not introduced as initial therapy. Fluconazole and itraconazole are triazole agents, formulated as capsules and suspension, and for both topical and systemic use. Fluconazole, also available for intravenous administration, is excellently absorbed across the gastrointestinal tract. Acidic environment is not required, while liver toxicity is rare at the therapeutic doses used.
Voriconazole, for per os or intravenous administration, is an azole sustained for deep-seated cases of candidosis. Posaconzole suspension is another triazole antifungal agent, under investigation against invasive fungal infections. Caspofungin (echinocandin) is another fungostatic agent against invasive fungal infections

Prognosis and complication

In most cases, oral candidosis has a good prognosis. Infection usually clears readily, after one or two weeks of antifungal treatment, especially when an early diagnosis has been achieved and the predisposing factor has been eliminated.

Recurrences may occur in patients at risk, with continuing presence of the predisposing factor.

In some patients, oesophageal candidosis may arise. Oral candidosis may be the first sign of oesophageal candidosis in AIDS patients. Candidosis may also develop and complicate head and neck radiotherapy or systemic cancer chemotherapy, causing diagnostic and therapeutic difficulties, since it is superimposed on radiation- and chemotherapy-induced mucositis. Prompt diagnosis and early treatment of oral candidosis has been found to significantly reduce the incidence of oesophageal candidosis.

In susceptible, immunocompromised and immunodeficient individuals, oral candidosis may extend regionally, while haematogenous, invasive hepatosplenic and other organ candidosis may occur as a life-threatening infection. Haematogenous candidosis is one of the most common nosocomial blood-stream infections with a high mortality rate. Prompt diagnosis and early treatment of oral candidosis has been found to significantly reduce the incidence of systemic candidosis.

Oral candidosis or increased numbers of *Candida* organisms may complicate and aggravate oral lichen planus and other autoimmune disorders of the oral mucosa Antifungal medication is recommended, by some authors, in oral *Candida* carriers with symptomatic lichen planus, either before or concurrently with corticosteroid medication.

Candida organisms may penetrate the epithelium of non-specific leukoplakia and candidosis may be superimposed on leukoplakia. Increased risk for dysplastic changes of leukoplakia has been attributed to the penetration by *Candida* organisms. Antifungal therapy may modify the clinical presentation of leukoplakia from non-homogeneous to homogeneous.

An important complication that has to be taken into consideration, in cases of persistent candidosis which require prolonged antifungal treatment, is the potential development of *Candida* strains resistant to antifungals.

Prevention

Identifying and correcting local or systemic predisposing factors, whenever possible, is the first step for the prevention of oral candidosis. Good oral hygiene, prosthetic rehabilitation and elimination of local irritants are essential.

However, specific groups of patients are particularly susceptible to the development of oral candidosis include:

Patients who receive topical or systemic corticosteroid or immunosuppressive treatment. These patients should be closely followed. Some authors have suggested the administration of antifungal prophylaxis, in oral *Candida* carriers, concurrently with the immunosuppressive medication, to prevent the potential development of oral candidosis.

HIV infected/AIDS patients, with CD4+ T lymphocyte counts below 200 cells/μL, who are not receiving a successful antiretroviral therapy. These patients are also at increased risk for oral candidosis, with potential regional extension and systemic dissemination. Antifungal prophylaxis may be needed to prevent candidosis in these patients.

Neutropenic patients or patients at risk for neutropenia, such as patients with leukaemia or other malignant haematological disease or solid cancer, who undergo chemotherapy or haematopoietic stem cell transplantation (bone marrow transplantation), are at increased risk for oral and oropharyngeal candidosis. In these patients, the oral cavity can serve as a site of colonization and infection, from which systemic candidosis may follow, causing significant morbidity and mortality. In leukaemic patients, who undergo transplantation, invasive fungal infection, mostly candidosis, may account for as many as 30% of deaths. Fluconazole prophylaxis has been found superior than oral polyenes and is recommended, being widely used to prevent candidosis in the above group of patients. Itraconazole oral solution has also been found to successfully prevent systemic fungal infections in children undergoing bone marrow transplantation and in adults with hematological malignancies.

Head and neck cancer patients who receive radiotherapy. At least one out of three of these patients are anticipated to develop oral candidosis, which will be superimposed on oral radiation-induced erythema and ulcerative/pseudomembranous mucositis. Oral candidosis, in those cases, will add to patients' discomfort during radiotherapy, while it will cause diagnostic and therapeutic problems, leading, at times, to unnecessary treatments.

The administration of antifungal prophylaxis to prevent oral candidosis during radiotherapy is under investigation. Preliminary results, with small numbers of study patients, have indicated that fluconazole prophylaxis may be of benefit.

The development of resistant *Candida* strains has to be taken into account in all antifungal prophylactic interventions.

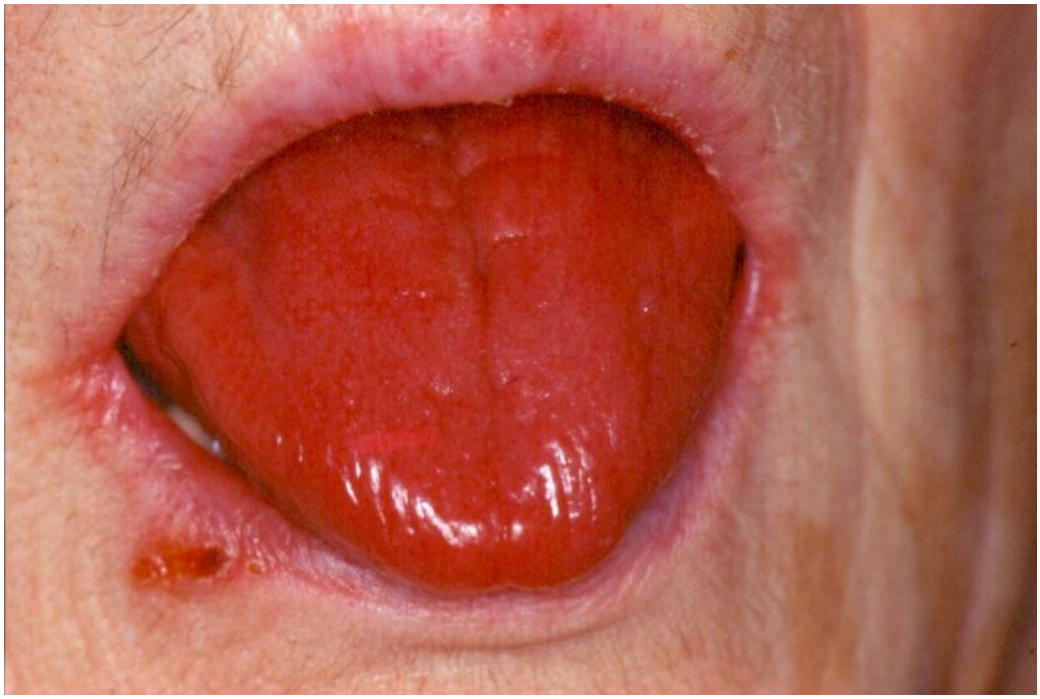

Figure 1. Acute, painful erythematous candidosis on the tongue of a 63 year-old female, after antibiotics.

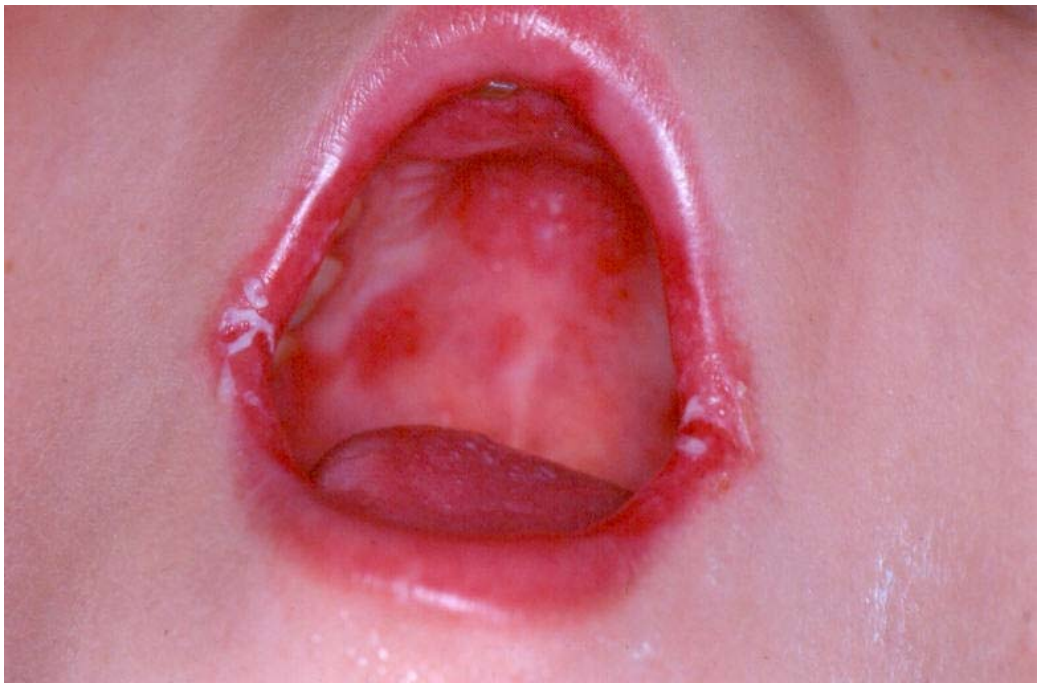

Figure 2. Erythematous candidosis on the palate of a 7 year-old girl, with vertical HIV transmission. Red patches can be observed. Candidal lesions (angular cheilitis) are also seen at the comissures.

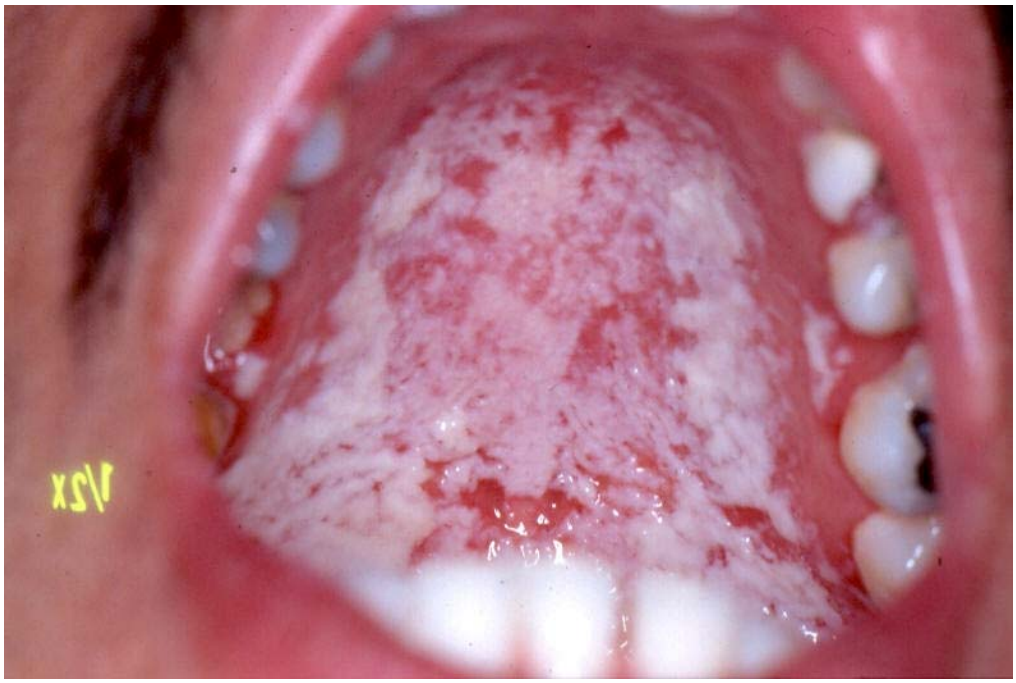

Figure 3 Pseudomembranous candidosis on the palate of a 26 year-old male with AIDS. Whitish, semi-adherent membranes and plaques, resembling curdled milk, can be observed.

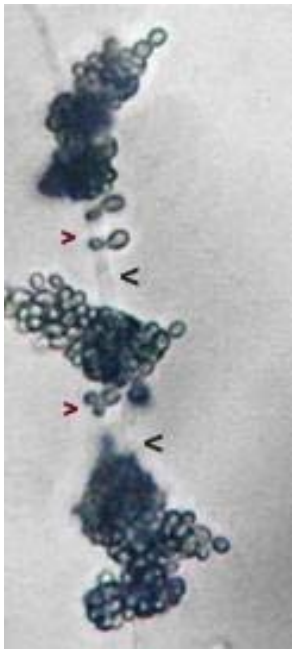

Figure 4. Microscopic morphology of *Candida albicans* pseudohyphae (black arrows) bearing clusters of single and budding yeast cells (red arrows) stained with lactophenol cotton blue. Microphotography with Nikon Eclipse 800. Courtesy of A. Velegraki, Mycology Reference laboratory, Medical School, University of Athens, Greece.

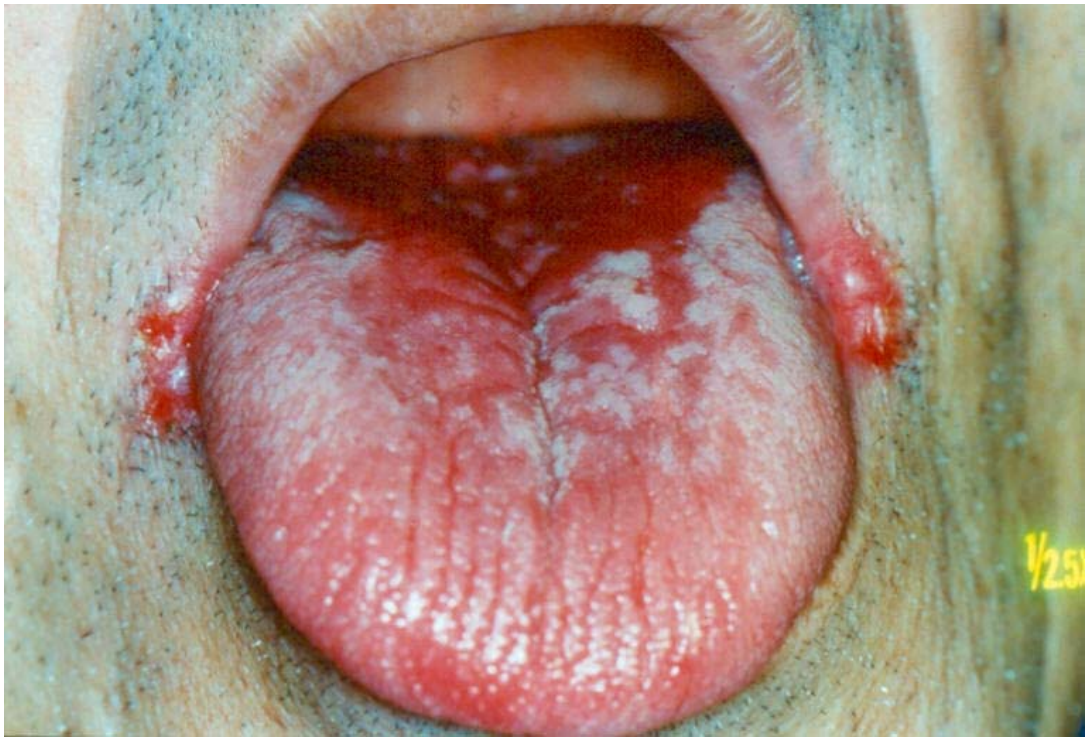

Figure 5. Angular cheilitis and erythematous candidosis on the tongue of a 69 year-old male. Patient wore dentures. Red fissures radiate from both comissures, while a red patch can be seen on the dorsum of the tongue.

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Links

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ORAL LICHEN PLANUS

Definition

Oral lichen planus is a common chronic inflammatory mucocutaneous disorder that typically affects the skin and/or mouth. Lichen planus can also affect other non-oral mucosal surfaces such as the genitals anus and pharynx, and rarely the conjunctiva and oesophagus.

Epidemiology

Lichen planus affects 1-2% of examined populations. It most typically arises in middle to late aged females, although can arise in childhood and adults. Oral lichen planus has a worldwide distribution. There appear to be no notable increased risks associated with particular ethnic groups.

Clinical presentation

Oral lichen planus has a bilateral distribution that typically affects the buccal mucosa, dorsum and ventral surfaces of the tongue and/or gingiva. Other mucosal surfaces can be affected but palatal involvement is particularly rare.

Oral lichen planus is often asymptomatic, although when there are areas of erosion or ulceration, the patient may have variable amounts of discomfort, being particularly troublesome when eating spicy or acidic type foods.

The variable clinical presentations of oral lichen planus comprise white patches, erosions, ulcers and, very rarely, blisters. The classification of the clinical presentation of lichen planus can be split into the following:

- Reticular oral lichen planus – this is the most common presentation, manifesting as a network of white striations. These lesions are often painless, although patients may complain of a slight roughness or dryness to the affected mucosal surfaces.
- Plaque-like oral lichen planus – this manifests as areas of homogenous whiteness. This typically arises on the buccal mucosa or dorsum of tongue and may be more prevalent amongst those who are smokers.
- Papular oral lichen planus – this manifests as small white raised areas approximately 1-2mm in diameter. These again typically arise on the buccal mucosa and dorsum of tongue, although may also present on other mucosal surfaces.
- Erosive oral lichen planus – this is sometimes termed atrophic oral lichen planus. In this form there are areas of redness within the aforementioned white patches. Patients with this type of disease often complain of oral soreness
- Ulcerative lichen planus – there are frank ulcers within the areas of whiteness. Patients complain of continued soreness, this being particularly severe with spicy or acidic foods.

- Bullous lichen planus – this rare presentation manifests as small vesicles or blisters (bullae) within the white patches.

Patients with disease involving the gingiva may have areas of white patches or striae superimposed upon redness of the gums. The latter is often termed desquamative gingivitis and can be extremely painful.

There is little predictability as regards the frequency of non-oral disease in patients with oral lichen planus. Likewise the oral features may precede, accompany or follow lichen planus affecting other sites.

Aetiopathogenesis

It is believed that oral lichen planus represents a cell-mediated immunological reaction within the affected tissues. The precise trigger for this is not known. The precise cause of oral lichen planus remains unclear in most cases.

Some patients appear to have an identifiable precipitating factor, and these are often termed lichenoid reactions. Occasional patients may have isolated areas of lichenoid reactions adjacent to amalgam restorations. Similar observations have been reported with dental restorations made of other metallic and non-metallic materials.

A small minority of patients may have lichenoid reactions that arise following drug therapy – particularly non-steroidal anti-inflammatory agents, beta-blockers, sulphonylureas, gold, penicillamine, allopurinol and occasionally anti-malarials.

Lichenoid reactions can arise in patients who have chronic graft-versus-host disease subsequent to bone marrow transplantation.

It has been suggested, but remains unclear, that there has been associations between oral lichen planus and hepatitis C virus infection. This association appears to occur more often in individuals living in areas of southern Europe, particularly Portugal, Spain and Italy. An association between hepatitis C virus infection and oral lichen planus has also been observed in individuals resident in Japan. Such associations may be related to the carriage rates of Hepatitis C in these parts of the world, or reflect some genetic predisposition to HCV-related oral lichen planus.

Diagnosis

The diagnosis of oral lichen planus is initially based upon the clinical presentation of bilateral white patches with or without erosions, ulcers or blisters, typically affecting the buccal mucosa, dorsum of tongue and gingiva.

Biopsy with subsequent histopathological examination of affected tissue is essential to exclude other disease that may mimic oral lichen planus – such as lupus erythematosus. In addition, it is advantageous to undertake a biopsy to identify possible areas of cellular atypia (dysplasia) within the involved tissue.

Treatment

Patients with white patches are generally asymptomatic, although they may complain of mild oral roughness, soreness or dryness of the oral mucosa. This generally does not require treatment. Individuals with erosive, ulcerative or bullous disease generally tend to have oral discomfort, particularly with spicy or acidic foods, and thus require treatment.

The management of painful oral lichen planus usually comprises:

- Relief of painful symptoms – this can best be achieved with regular use of benzydamine hydrochloride (0.15%) spray or mouthrinse. When this is not available, it may be appropriate for the patient to apply 2% lidocaine gel to painful areas;
- Treatment of definitive disease – topical corticosteroids are the mainstay of treatment of oral lichen planus. A wide range of agents are suggested to be effective . These include:

    Triamcinolone acetonide (0.1%) and 1% carboxymethylcellulose paste

    Betamethasone mouthrinse (500mcg dissolved in 10-15ml of water) used as a mouthrinse up to 3 times daily

    Fluticasone spray (50mcg per puff) – sprayed on affected areas up to 3-4 times daily

    Prednisolone mouthwash (5mg dissolved in 10-15ml of water) and used as a mouthrinse up to 4 times daily

    Beclometasone spray (100mcg per puff) – sprayed 3-4 times daily on affected sites

    Clobetasol ointment (0.05%) applied to painful areas 3-4 times daily

    Fluticasone cream (0.05%) applied to painful sites 3-4 times daily

Where disease appears to be recalcitrant to such therapy, a number of other strategies may be considered:

Topical tacrolimus (0.1%) applied to painful areas twice daily

Ciclosporin mouthwash (100mg per ml) used as a swill and spit mouthwash twice daily

Severe disease may warrant short-term systemic corticosteroid therapy (e.g. prednisolone or deflazacort), with additional corticosteroid-sparing immunosuppressant regimes such as azathioprine. Patients with symptomatology affecting other mucosal surfaces or the skin require referral to appropriate specialist for further evaluation.

Prognosis and complications

Oral lichen planus persists for many years, resolving rarely. The principle aim of treatment is to heal areas of painful erosion, ulceration or blistering.

Long-standing oral lichen planus rarely gives rise to any notable complications, however, there is some concern that lichen planus of the mouth may have some malignant potential. This possible association with oral squamous cell carcinoma remains controversial. Although there have been many studies examining the malignant potential of oral lichen planus, most have been retrospective, and

some have not described the disease in any great detail. In addition patients have developed oral squamous cell carcinoma at sites distant to those affected by lichen planus.

It is presently suggested that 1-3% of patients with long-standing oral lichen planus may develop a squamous cell carcinoma of the mouth. Whether this reflects a common cause or that lichen planus does indeed predispose to oral squamous cell carcinoma remains unclear –lichen planus is common, and an association with squamous cell carcinoma might be coincidental.

In view of the controversy regarding the malignant potential of lichen planus, it is recommended that all patients are regularly reviewed by a health care provider for changes suggestive of potential malignancy of the oral cavity. Isolated areas of increasing whiteness, redness, speckling (areas of redness and whiteness) or solitary ulceration unlikely to reflect local trauma require further specialist investigation (usually by histopathological investigation of lesional tissue).

All patients with oral lichen planus should be advised of the controversy regarding the malignant potential of oral lichen planus, and provided with appropriate preventative advice – particularly the avoidance of tobacco and alcohol and betel, and empirically a diet rich in vitamins A, C and E and the maintenance of good oral hygiene.

Prevention

At the present time, as the cause of lichen planus is unknown, there is no specific preventative programme for this disorder. Likewise there remains no evidence that modification of diet or oral hygiene will lessen the possible development of symptomatic disease. However, regular clinical review is important in view of the controversy regarding the malignant potential of this disorder.

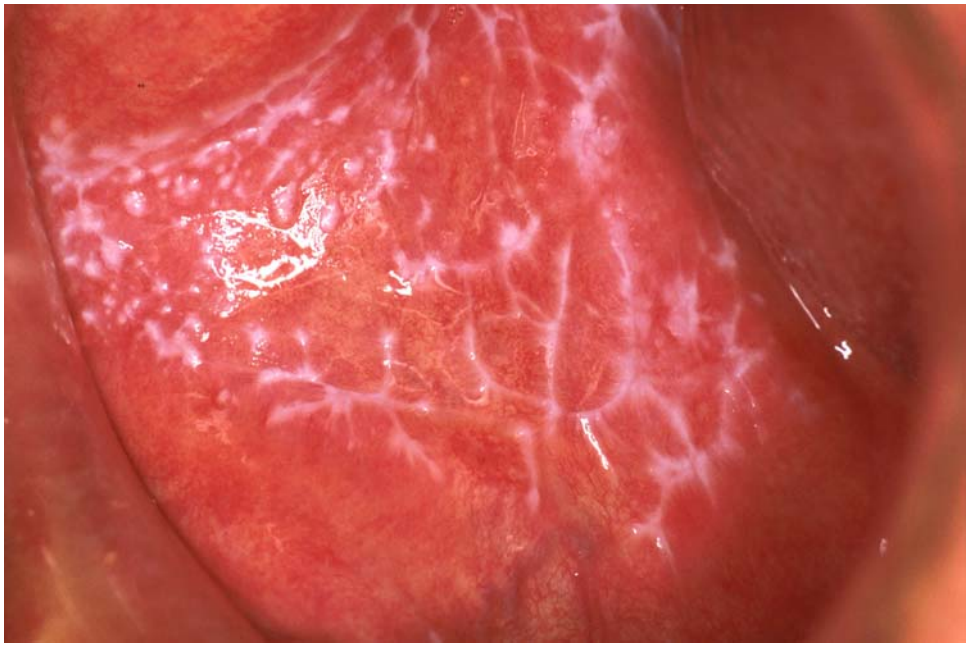

Figure 1. Lichen planus: reticular lesions of the oral mucosa

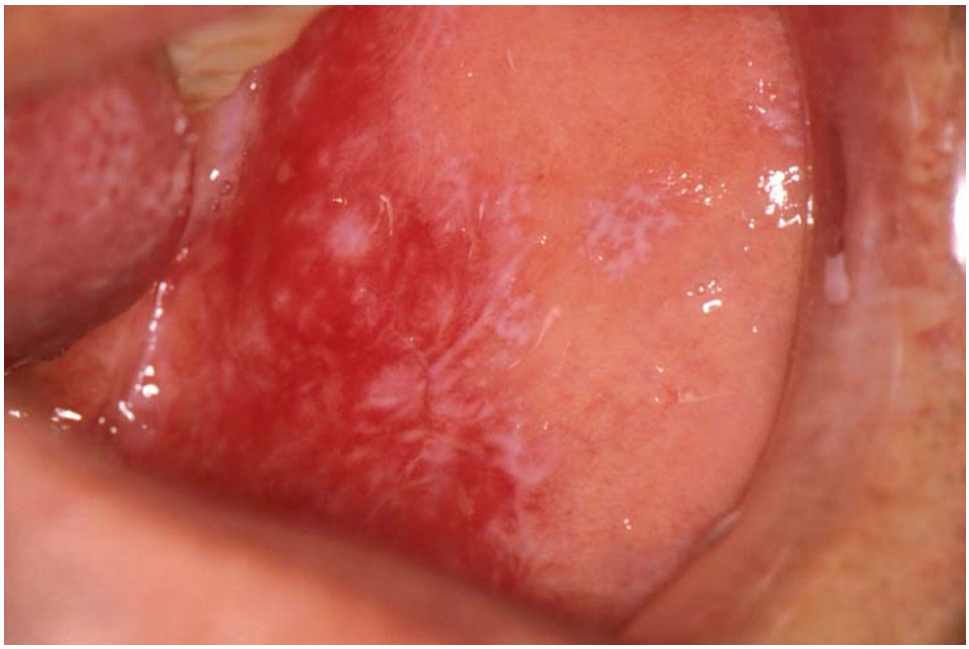

Figure 2. Lichen planus: atrophic lesions of the oral mucosa

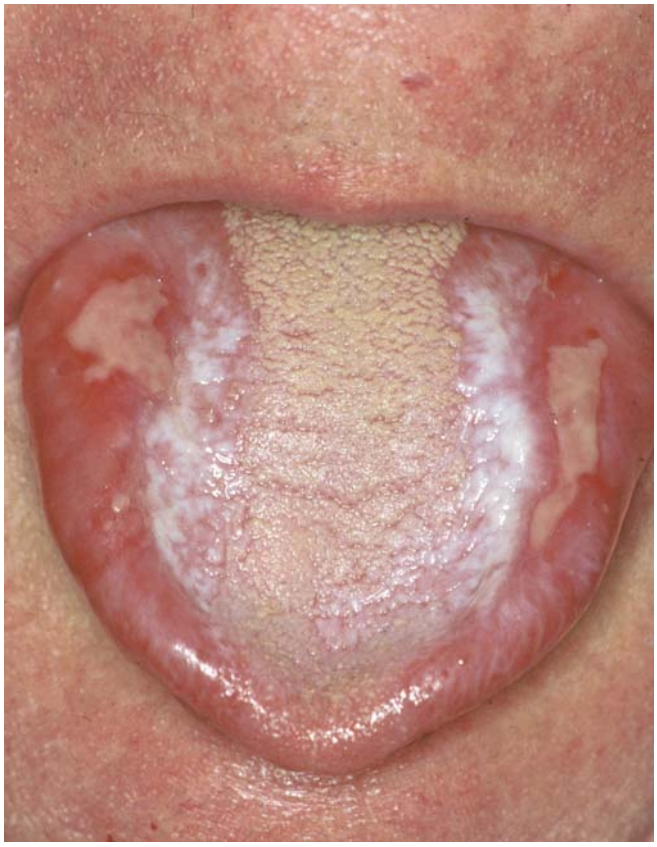

Figure 3. Lichen planus: plaque like lesions and erosions of the tongue

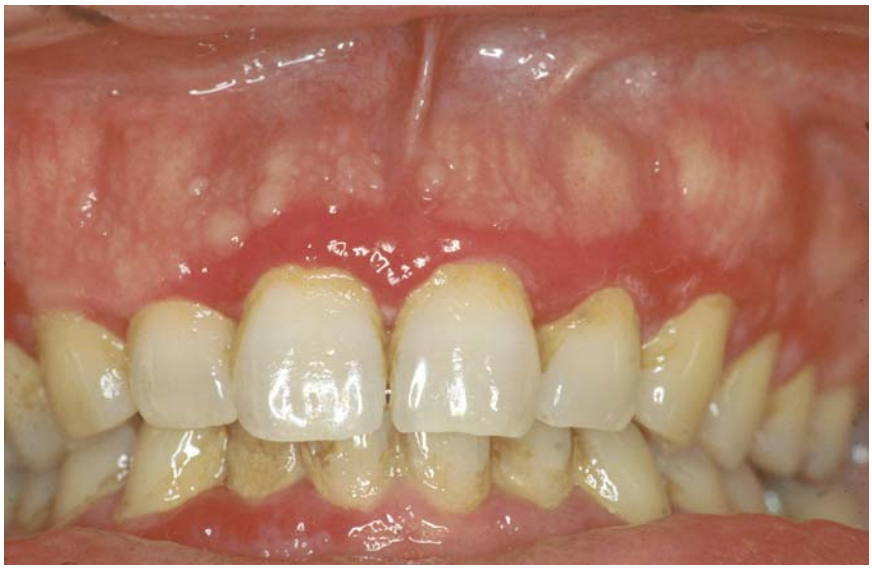

Figure 4. Lichen planus: desquamative gingivitis

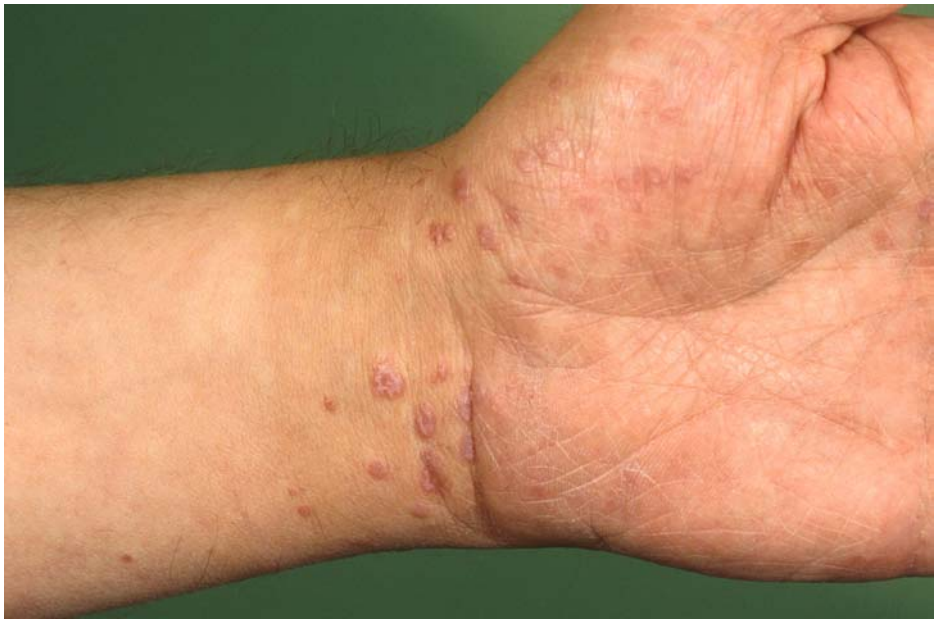

Figure 5. Lichen planus: skin lesions

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ORAL LUPUS ERYTHEMATOSUS

Definiton

Lupus erythematosus (LE) is an autoimmune disorder, in which the body's own immune system attacks its own tissues, especially components of the cellular nuclei. *Lupus* is the latin for wolf and *erythematosus* indicates red-like. Thus, LE stands for ”the red wolf” which should be in contrast to *lupus vulgar*is, ”the common wolf” which in the old days designated the skin of the face in patients with cutaneous tuberculosis.
There are two main forms of lupus, discoid LE (DLE), affecting skin and mucous membranes, and systemic LE (SLE), which may also affect joints, visceral organs and other tissues. The classification may now also include a bullous form, a neonatal form (NLE), an acute cutaneous form (ACLE), a subacute cutaneous form (SCLE) and a chronic cutaneous form (CCLE). There is also a special subgroup of SLE with very early onset, childhood-onset systemic lupus erythematosus, cSLE. In addition, there is probably a drug-induced, and thus potentially reversible form of LE.

Epidemiology

LE affects women 9-10 times as frequently as men and is most prevalent in ages from 18 to 65 years with a peak between 25-45 years, although it has been found in children of 10 years of age. At older ages the gender difference seems to be considerably reduced. SLE may affect up to one white person in 2500 people and one out of 250 African American women. Also Asians show relatively high prevalence figures. The different forms may change in the same person. Thus, DLE may develop into SLE in about 20% of the cases. The occurrence of oral mucosal lesions in LE patients is about 25-75% in different studies. Arthralgia is the most prevalent finding, 65%, and cutaneous lesions are encountered in about 25%.

Clinical presentation

The best-known sign of LE is the so-called facial butterfly rash, most frequently seen in SLE. Other manifestations seen on the skin are vasculitic dermatitis, often seen on the fingers and behind the ears, maculopapular eruptions, Raynaud’s phenomenon and alopecia.The erythematous skin lesions comprise well-defined patches with adherent scaling. SLE may show an array of features including fatigue, involvement of the

kidneys, the heart, lungs and brain, joint and muscle pain, depression and also anemia. The arthritis is symmetrical and similar to rheumatoid arthritis.
Most patients with LE are sensitive to sunlight which can aggravate rashes. Severe aggravation with ulcerations may e.g. be found on the vermilion border.
Similar oral mucosal lesions are seen in DLE and SLE. The typical lesion comprises a central erythematous mucosa surrounded by a slightly elvated white border. This border is characterized by fine perpendicular white ”paint-brush”-like lines. The lesions are most often found in the palate and in the buccal and vestibular mucosa. About 50% of the lesions are Candida-infected. Some lesions, especially in the palate, may though be quite ”unspecific” just appearing as ill-defined superficial ulcerations. About 75% of the patients complain of oral symptoms e.g. dryness, soreness and a burning sensation especially when eating hot and spicy food.
SLE is closely associated with excretory gland involvement. Thus, oral and ocular symptoms are frequent findings. Minor salivary gland lymphocytic infiltrates are found in 50-75% of the patients, whether they are complaining of dry mouth or not. Unstimulated salivary flow rate is decreased in many of the SLE patients. Also SLE is a diagnostic component of secondary Sjögren’s syndrome.

Aetiopathogenesis

The cause for LE is, as for many autoimmune disorders, unknown. In the development from ”damage” or initiation to clinical appearance, production of circulating autoantibodies to nucleoproteins, antinuclear antibodies (ANA), is the basic event. The initiating process is unknown but possibly a mutation in a gene associated with natural cell death (apoptosis) and making lymphocytes recognize self and not-self molecules is involved, permitting autoreactive lymphocytes to circulate and to attack the own body cells. Another theory might be that LE autoantibodies are a sequelae of cross reactions to exogenous antigens e.g. RNA retroviruses. Factors such as exposure to sunshine, infections and drugs may trigger SLE reactions in some patients. Whatever the aetiology, there seems to be a genetic predisposition, expressed as associations with specific HLA/MHC antigenic profiles.
One main defect in SLE is dysfunction of B-lymphocytes. Also suppressor T – lymphocytes are reduced in number, permitting a considerable increase in autoantibodies. As result of the contact between the autoantibodies and the body’s own cells immune complexes appear. The main pathology is mediated via these immune

complexes which are deposited in e.g, blood vessels, glomerular basement membranes and skin. The complexes activate the complement system thereby releasing lysosomes and an array of cytokines leading to malfunction/ damage in the organs where the complexes are deposited.

Diagnosis

The oral manifestations of LE may be difficult to differentiate from lichen planus lesions. However, palatal lesions are more common in LE than in lichen planus. A typcal skin biopsy specimen of DLE and SLE may show hyperkeratosis with follicular keratin plugging, acanthosis, liquefaction degeneration of the basal epidermal layer and thickening of the basement membrane. Further, there are heavy lymphoid aggregates around blood vessels and close to the basement membrane. In oral lesions these perivascular infiltrates are less pronounced and instead the submucosal lympocytes show a bandlike appearance. Immunofluorescence may demonstrate PAS-positive thickening of vascular membranes and a broad PAS-positive subepithelial band – sometimes called a lupus band. However, the histopahology is not specific and may be difficult or impossible to differ from characteristics compatible with a lichen diagnosis.
In SLE circulating, autoantibodies are almost always found and the diagnosis may be supported by identifying one or more of them. Antinuclear antigen, ANA, may be found in >95%, anti-double stranded DNA in 40-60%, anti-Ro (anti-SSA often found in Sjögren's syndrome) in 30-40% and anti Smith antigen in 20-30%. However, of these autoantobodies only anti-DNA and anti-Sm are to some extent specific for LE.

Treatment

LE may show manifestations in and symptoms from many organs in the body and systemic treatment is therefore required. The drug of first choice is the antimalarial hydroxychloroquine, especially in patients with polyarthralgia and skin manifestations. This treatment carries a small risk for developing retinopathy which is reversible after the drug has been withdrawn. There also a risk for oral mucosal melanin pigmentation. In cases of LE skin lesions sun block for UVA and UVB is important. Treatment may be supplemented or changed for combinations with topical and systemic corticosteroid. Systemic steroids are used in more severe cases of LE. Sometimes methotrexate or azathioprine may be used as steroid-sparing drugs. Thalidomide has a good effect on

DLE lesions but is most often avoided because of its teratogenicity and the risk of neuropathies.
Oral manifestations of LE do not always resolve after the systemic treatment. Additional topical treatment may then be applied. Since oral LE lesions are frequently infected by Candida, antimycotic treatment should be given (see chapter on Candidosis). Such treatment could also preferably be given supplementary to systemic treatment with immunosuppressive drugs. After some days of antimycotic treatment (which should be continued for 2-4 weeks), topical steroids should be used similar to those recommended for oral lichen lesions (see chapter on Lichen planus).

Prognosis and complications

So far there is no cure for LE. Renal disease causes the majority of morbidity and mortality, and in some cases dialysis and kidney transplantation may be necessary. Up to 85% of patients with SLE may suffer from blood disorders including thrombocytopenia and haemolytic anemia. Complications also include strokes, pulmonary embolism or abortion. Pericarditis, endocarditis and myocarditis may develop. In order to follow disease activity, including also predicting damage and steroid requirements, activity acouple of indices have been developed and evaluated - the Systemic Lupus Erythematosus Activity Index (SLEDAI) and European Consensus Lupus Erythematosus Measurement (ECLAM).
The 10-year survival for LE exceeds 85%. Mortality rate for LE is thus low, apart from severe cases of disseminated LE with a mortality rate of about 15%.
Oral ulcerative discoid lesions have been considered to be precancerous/potentially malignant.

Prevention

Since the cause of LE is unknown, the possibility for prevention of the outbreak of the disorder *per se* is highly questionable. It has been suggested that risk factors that are likely to signal transition of cutaneous into systemic LE are high ANA titers (> 1:320) and the presence of arthralgias. Cutaneous LE patients who exhibit these symptoms should be monitored closely, since they may be at increased risk to develop SLE.
Some preventive measures may be taken to reduce signs and symptoms as well as side effects of administered therapeutic drugs. Sunglasses, sunscreen, protective clothing and oils to protect the skin from UV light may prevent or reduce skin rashes and possibly

nausea. Medication with steroids may prevent flare-up of polyarthritis and skin lesions. However, all patients on long-standing high doses of systemic corticosteroid therapy are at risk for the development of osteoporosis, which may occur in more than half of the patients with SLE. In order to prevent this development, steroid doses should be reduced to a minimum and the patient should be given calcium, vitamin D, calcitonin and possibly also bisphosphonates.

Pictures

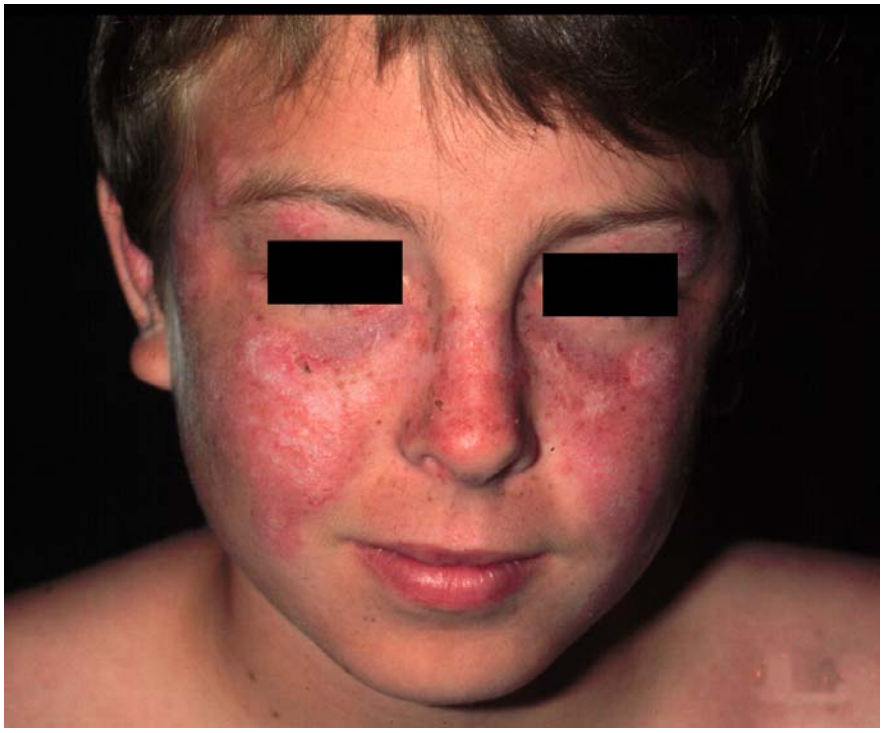

Figure 1. 13 year old girl with butterfly erythema

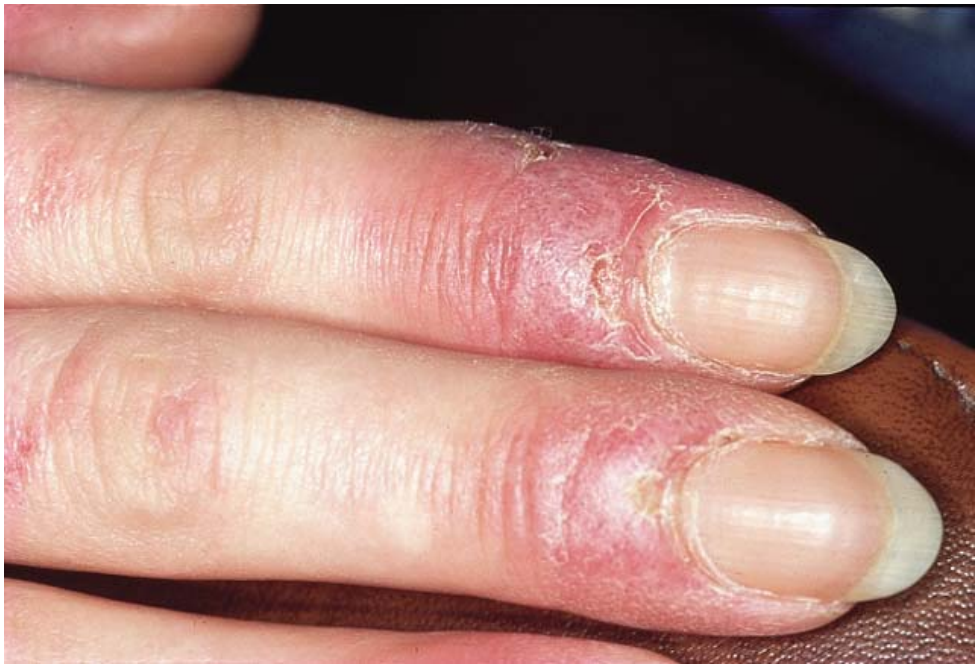

Figure 2. Fingers with vasculitis and Raynaud's phenomenon

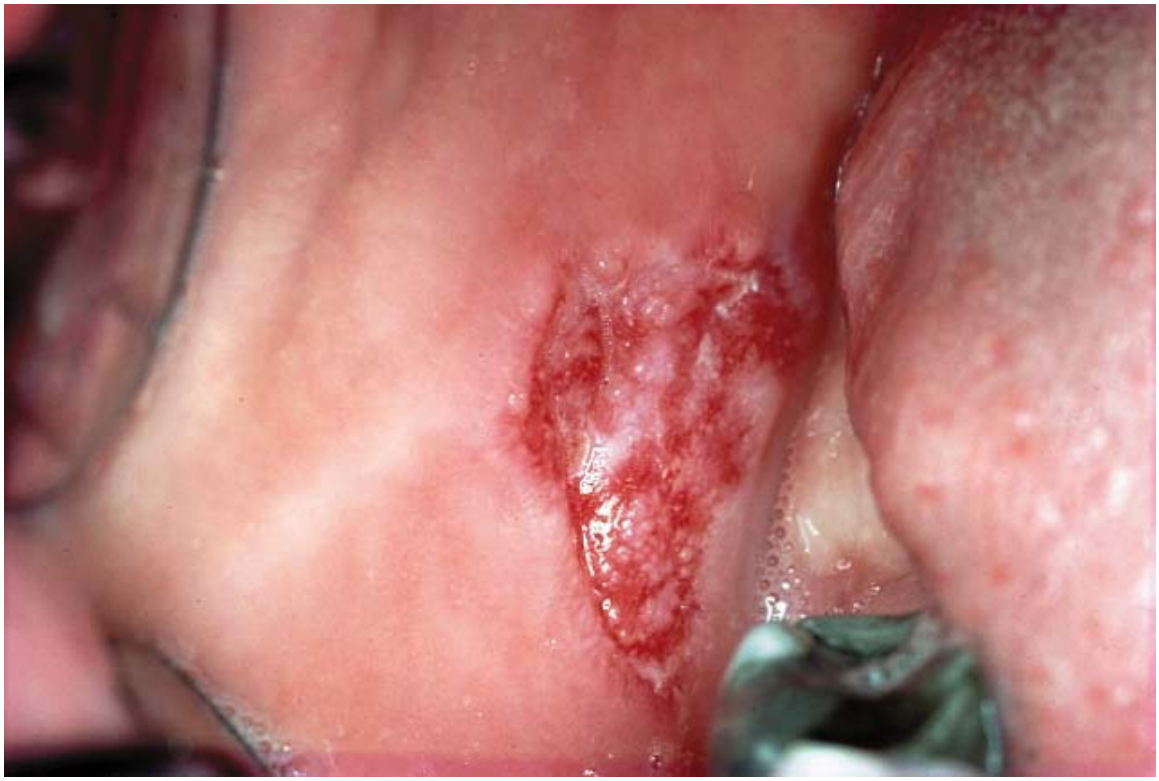

Figure.3. Discoid lesion in the buccal mucosa

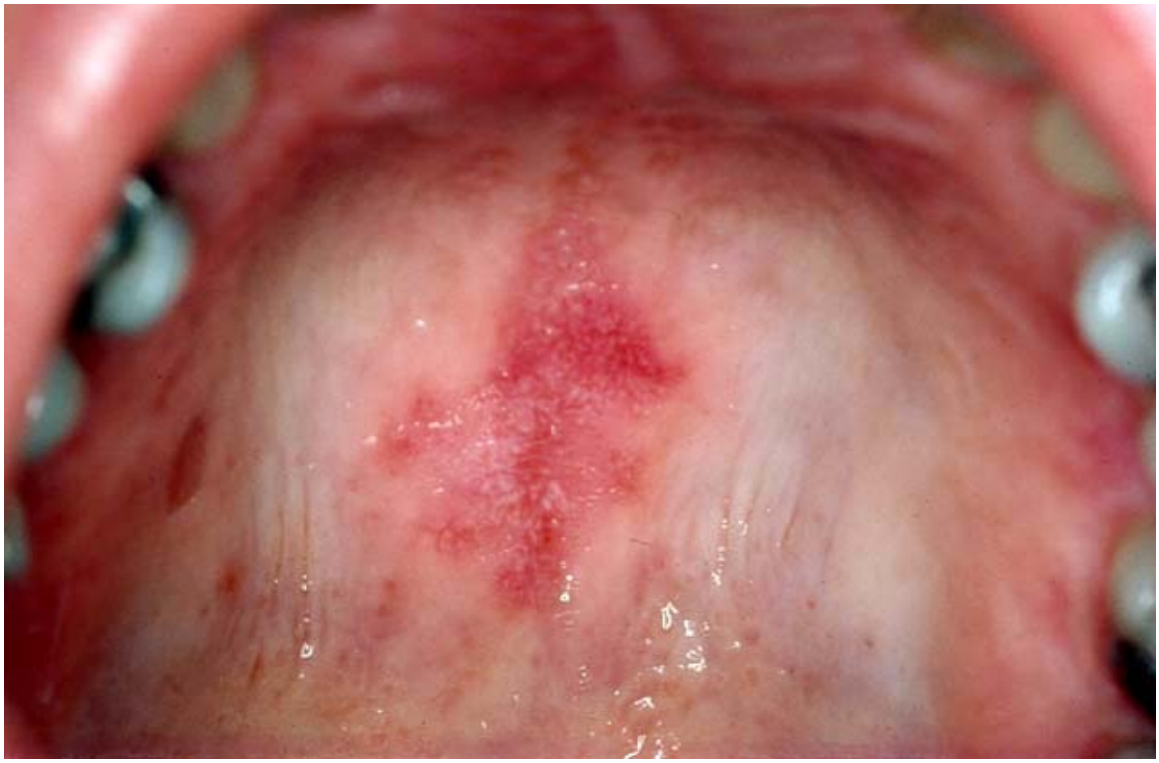

Figure 4. Palatal lesion

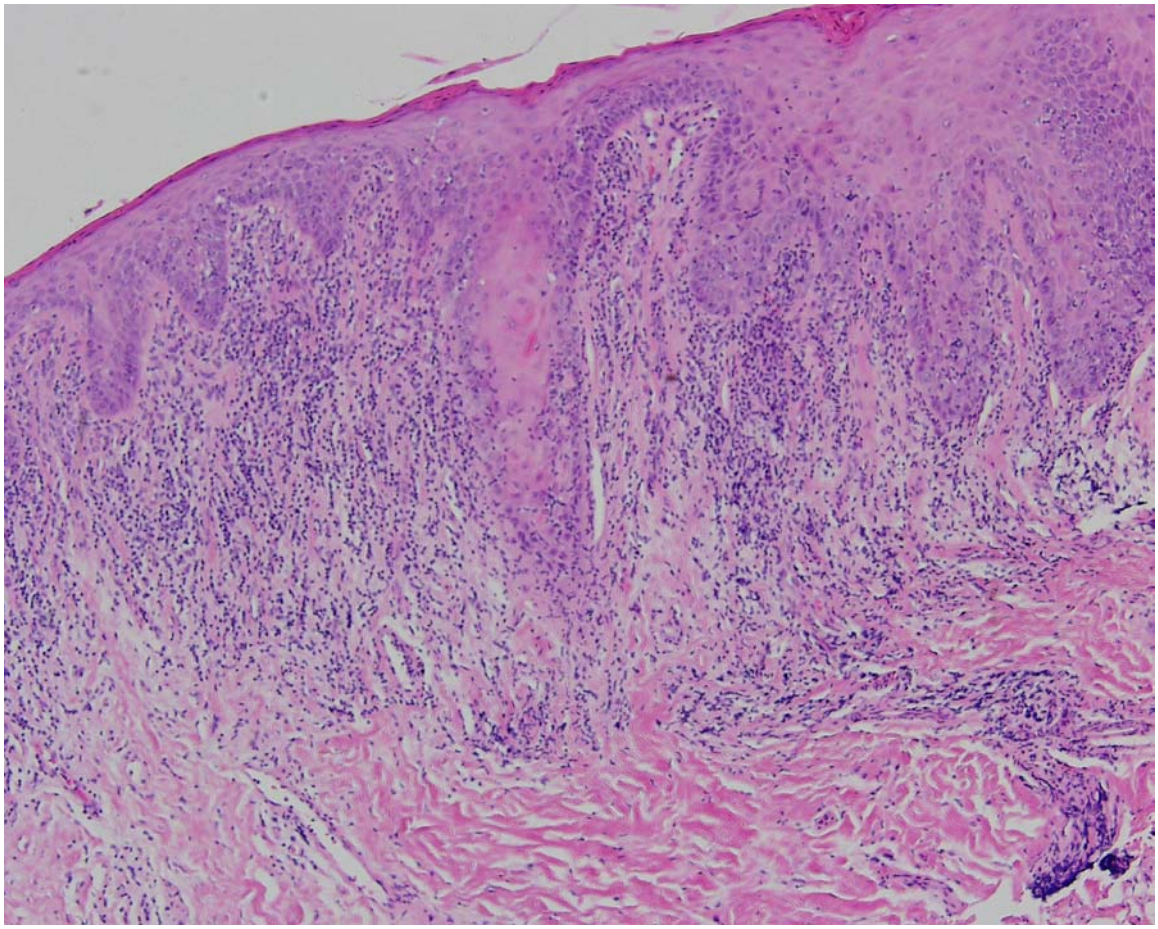

Figure 5. Histologic picture of LE

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www-medlib.med.utah.edu/WebPath/TUTORIAL/SLE/SLE.html

ORAL MALODOUR

Definition

Oral malodour (halitosis or breath odour; from the Latin for breath, *Halitus*), is a fairly common complaint that affects personal relationships and quality of life. Though the true prevalence is unclear, up to 30% of adults over 60 years of age report either being conscious of their oral malodour, or having been told by others they have it. In most cases, oral malodour is related to tongue microbial metabolism of local debris.

Clinical features

Oral malodour can be difficult to perceive by the patient. There is no current objective method of self-assessing the degree of oral malodour. In some cases, patients present halitophobia, a self-conviction to have bad breath not supported by objective analysis.
Many patients adopt a number of behavioural measures to minimise their perceived problem, such as using chewing gums, mints, mouthwashes or sprays designed to reduce malodour, cleaning their tongue repeatedly, covering their mouth when talking, avoiding or keeping a distance from other people, and avoiding social situations.

Aetiopathogenesis

The basic causes of oral malodour are now fairly well understood. There are different degrees of oral malodour, and some situations are part of normal physiology.

1. Morning breath

When oral malodour is common on awakening (so called *morning breath*), this is usually a consequence of low salivary flow and stagnation during sleep. This complaint can be higher in mouth breathers and may be exacerbated by other oral causes of malodour.
If this is the case, oral malodour may be readily rectified by eating, tongue brushing, tooth brushing and rinsing the mouth with fresh water. Hydrogen peroxide rinses will also eliminate this odour.

2. Exogenous malodour

Various foods such as garlic, onion, durian, cabbage, Brussel sprouts, cauliflower or raddish, spices such as in curries, as well as habits such as tobacco or alcohol can cause bad breath. Avoidance of these foods and habits is the best mean of prevention.

3. True oral malodour (endogenous malodour)

When oral malodour is not associated with the factors already described, it is most often a consequence of oral bacterial activity, typically from anaerobes. There are many reasons for this bacterial activity, first of all poor oral hygiene.

However, some bad breath seems to be associated with local pathological causes, such as gingivitis (especially ANUG), periodontal disease, infected extraction sockets, or other types of oral sepsis.
In some cases, other possibilities that favour oral malodour are the presence of residual blood post-operatively, debris under bridges or appliances, ulcers, dry mouth and putrefaction of postnasal mucus drip stagnating on the tongue.
The large surface of the tongue and its papillary structure retain a consistent number of food debris and are often the location of the micro-organisms implicated which are predominantly Gram-negative anaerobes, and include *Porphyromonas gingivalis*, *Prevotella intermedia*, *Fusobacterium nucleatum*, *Bacteroides forsythus* and *Treponema denticola*.
In many instances, these bacteria release chemicals that produce malodour, which include volatile sulphur compounds (VSC) such as hydrogen sulphide and methyl mercaptan, but also diamines like cadaverine and putrescine and short chain fatty acids (butyric, valeric and propionic).
Recently, Gram-positive bacteria have also been implicated since they can denude the available glycoproteins of their sugar chains, enabling the anaerobic Gram-negative proteolytic bacteria to break down the denuded proteins, resulting in the chemicals described above. On the other hand, the evidence for the implication of other micro-organisms, such as *Helicobacter pylori*, is scant.
Smoking may increase the production of some of these odiferous compounds and smoke itself contains thousands of volatiles.
In the absence of oral causes, systemic conditions may be responsible for oral malodour, including starvation, drugs causing dry mouth, drugs like cytotoxic agents, dimethyl sulphoxide, disulfiram, nitrites/nitrates and solvent abuse.
A part from local causes, the most common source of bad breath is the nose and its passages. Respiratory diseases that should be ruled out include nasal sepsis or foreign bodies, paranasal sinus infection, tonsillar infection, lower respiratory tract infection and infected tumours in the respiratory tract.
Other systemic causes of halitosis are less common and they include diseases such as diabetes mellitus and gastrointestinal diseases. Gastroesophageal reflux disease (GERD) may occasionally underlie halitosis, as well as hepatic failure and renal failure.
One interesting but rare situation is trimethylaminuria (TMAU; fish malodour syndrome). Trimethylamine (TMA) is present in the diet or can derive from the intestinal bacterial degradation of foods such as fish, eggs and some legumes rich in choline and/or carnitine. TMA is normally oxidized by the liver to the odourless trimethylamine-N-oxide (TMAO) which is then excreted in the urine. Inherited mutations of the gene for a liver drug-metabolizing enzyme (the flavin-containing monooxygenase 3 - FMO3)) accounts for a severe recessive

form of trimethylaminuria in which there is impaired oxidation of TMA. The unoxidized TMA is excreted in urine, sweat, vaginal secretions, saliva and breath. Rarely a similar problem can arise due to congenital liver disorder with portal-systemic shunting due to an unusual intrahepatic vascular connection.
Halitophobia is a psychogenic condition. In these patients, no evidence of halitosis can be detected even with objective testing, and the condition may be attributable to a form of delusion of monosymptomatic hypochondrias.

Diagnosis

Diagnosis of this condition is mainly clinical. A full history must be collected together with a clinical examination. Assessment of the presence and degree of halitosis can be simply performed by smelling the exhaled air (*organoleptic* method) coming from the mouth and nose and comparing the two.
It is also possible to perform objective measurements of the responsible volatile sulphur compounds such as hydrogen sulphide and methyl mercaptan, using a *halimeter* (Interscan Corp., Chatsworth, CA, USA) or similar device. Other gaseous compounds however, are not detected, and therefore this is not entirely accurate.
The quality of the oral flora may also be assessed by using the BANA (benzoyl-arginine-naphthyl-amide) test or darkfield microscopy. To exclude the rare situation of trimethylaminuria, analysis of urinary excretion of trimethylamine and of trimethylamine-N-oxide usually by gas chromatography or direct proton NMR spectroscopy can be performed.

Management

There is no specific treatment, rather a workout of potential causes and a number of measures to be performed by the patient and the clinician. Diagnosing and treating any underlying dental, oral, ENT or medical cause must of course precede any other approach. Very importantly, patients must be educated to take regular meals and to avoid smoking and odiferous foods. Moreover, oral and denture/appliance hygiene is mandatory, to be performed by toothbrushing, flossing and by tongue cleaning with a scraper.
Oral antiseptics with chlorhexidine, cetylpyridinium chloride, triclosan, essential oils, or zinc chloride and chlorine dioxide are also effective at reducing malodour, in most cases for at least 3 hours. Chewing gum to increase salivation and using breath freshening preparations may be of help.
Only in recalcitrant cases, an empirical one week course of metronidazole 200mg three times daily can be useful.

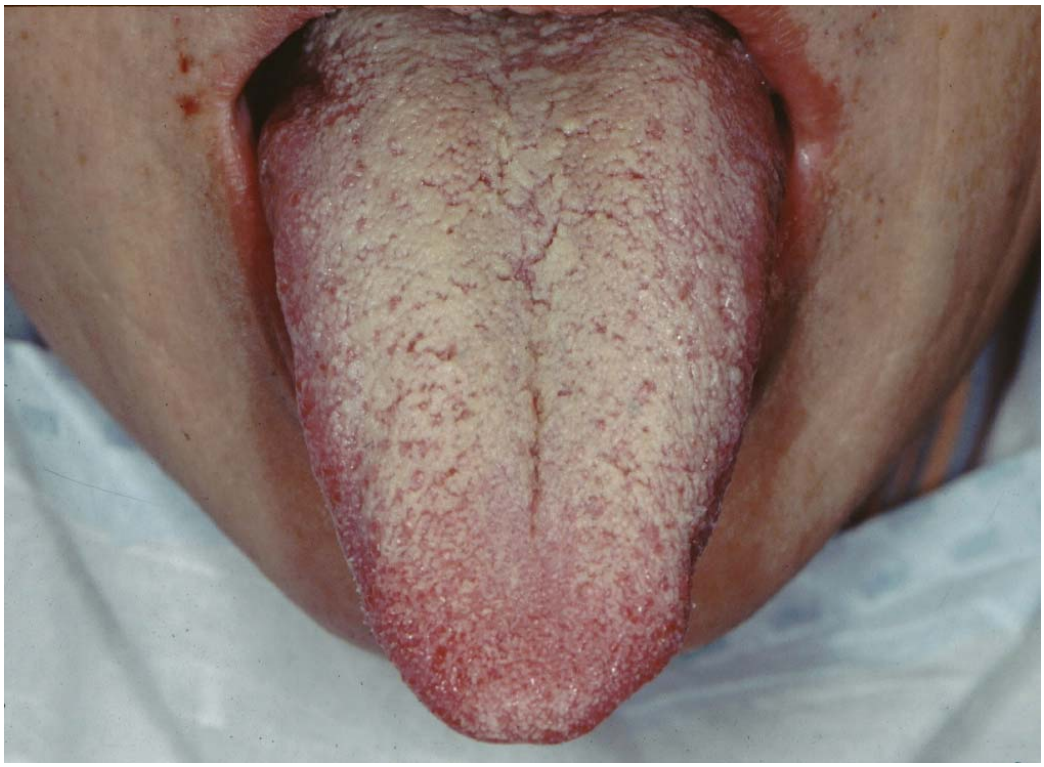

Figure 1. Heavy coating of the tongue dorsum, composed by organic debris and bacterial biofilm which is the main source of oral malodor

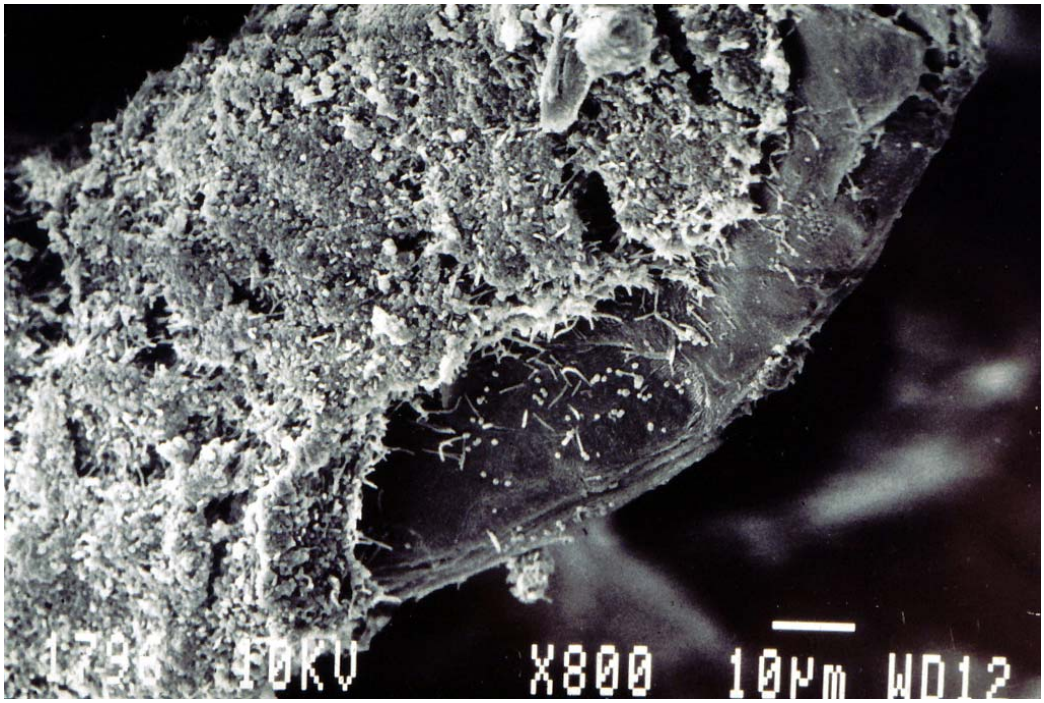

Figure 2. Scanning microscopy of the tip fof a human filiform papilla. A thick composite bacterial biofilm is visible on the epiithelial surface.

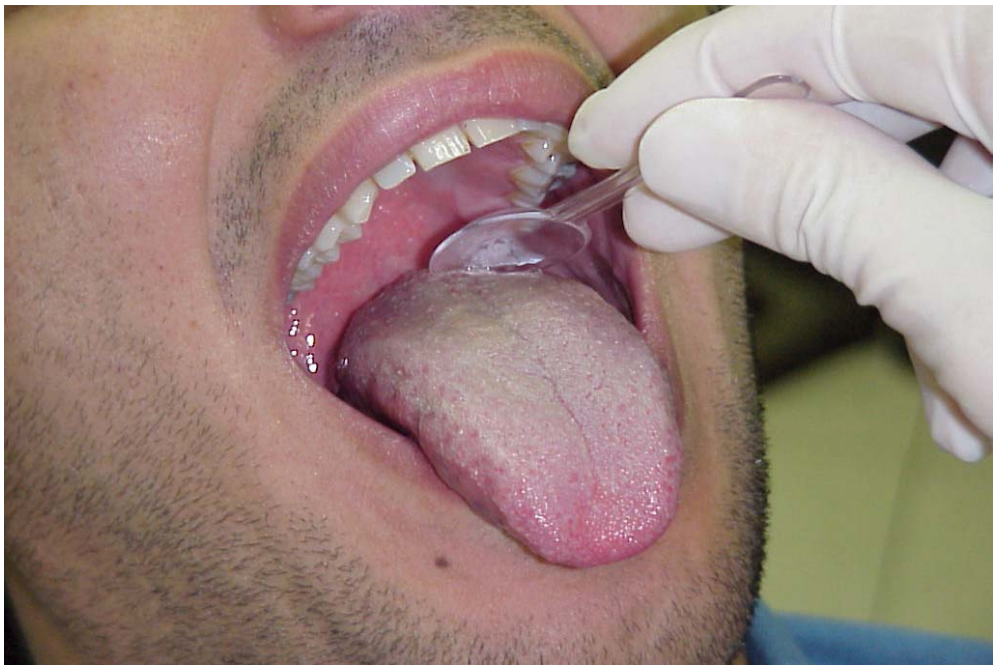

Figure 3. With the “spoon test” the coating of the posterior tongue dorsum could be collected and assessed by the clinician to determine organoleptically the intensity of patient halitosis

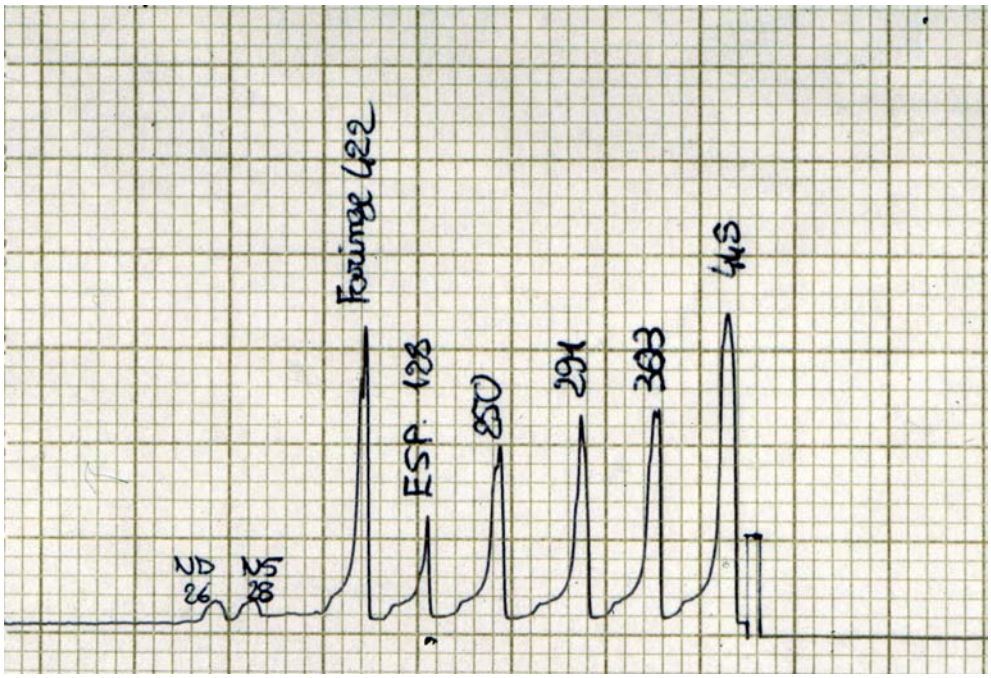

Figure 4. Electrochemical analysis of VSC content of the mouth, pharingeal and nasal atmosphere obtained with the Interscan Halimeter® measuring device.

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ORAL MELANOMA

Definition

Melanoma is a highly malignant neoplasia, arising from melanocytes, the cells that produce the brownish pigment melanin. Melanin is the determinant in skin colour and protects against ultraviolet (UV)-A and UV-B irradiation from the sun. As most fair-skin individuals grow older, melanocytes often proliferate, forming concentrated clusters that appear on the surface as small, dark, macular or nodular spots, which are usually harmless. When cell proliferation occurs in a controlled and contained manner, the resulting lesion is benign and termed *naevus*. Sometimes, melanocytes grow out of control, producing irregularly pigmented, asymmetrical and poorly demarcated lesions, suggesting that malignant transformation has occurred, in the form of a life-threatening disease called *melanoma*. Sometimes, melanoma manifests suddenly as a rapidly growing mass without any preceding naevus.

Epidemiology

The most common sites for mucosal melanomas are the head and neck region, followed by anal/rectal region, female genital tract, and urinary tract. Primary malignant melanomas of the oral squamous mucosa are rare, accounting for approximately 0.3-2% of all malignant melanomas, about 4% of head and neck melanomas and 0.5% of all oral malignancies. The low prevalence of primary oral melanoma is in contrast to cutaneous melanoma which has been increasing by 4–6% per year since 1973, with 41,600 new cases diagnosed and 7200 melanoma-related deaths in 1998 in the US.

Patients affected by oral melanomas are typically older and a decade earlier in males than in females. Melanomas may be found more frequently in men, with a male-to-female ratio of almost 2:1, but gender distribution varies, depending on geographic location. Mucosal melanomas are relatively common in Japan, with the oral cavity being the most frequent site, whereas, melanoma of the skin is less common in Japanese than in Caucasians.

Clinical Presentation

Oral melanoma may present either as a rapidly-developing pigmented lesion or as a tumour preceded by a pigmented area for a variable period of time. Lesions may be single or multiple, macular or nodular, with variable colour and shape, and can be either primary or metastatic. Associated symptoms which are not specific for melanoma but are shared by a number of other primary tumours of the oral cavity

include ill-fitting dentures, loose teeth, bone loss, bleeding and mucosal ulceration. Oral melanoma may equally arise from neoplastic transformation of either melanocytes or naevus cells although intra-oral nevi are uncommon and their malignant transformation is less substantiated than their skin counterparts. Intra-oral nevi are often seen on the hard palate and less frequently in the buccal and labial mucosa, gingiva and alveolar ridge, and may present as small, flat or elevated macules or papules, that may also be non-pigmented. Similarly, oral melanomas have also a decided predilection for the palate, followed by the maxillary gingiva. Non-pigmented forms of malignant melanoma often present as soft, vascular tumours, that cannot be distinguished clinically from other benign or malignant oral tumours and in such cases the histopathological examination is essential to establish a definitive diagnosis.

Aetiopathogenesis

The key to understanding the process by which melanocytes are transformed into malignant melanoma seems to lie in the interplay between genetic factors and the UV spectrum of sunlight, although the nature of this relation has remained obscure. Recently, prospects for elucidating the molecular mechanisms underlying such gene-environment interactions have brightened considerably through the development of UV-responsive experimental animal models of melanoma. Genetic factors remain as the likely causative agent for oral melanomas. In fact, it has been demonstrated that point mutations in P53 tumour suppressor gene may be associated with mucosal melanomas. Nonetheless, probably, one of the major reasons for the lack of understanding regarding mucosal melanomas is the rarity of this malignancy. This contributes to difficulties in searching a sufficient number of cases to evaluate on a scientific and standardised manner, and its aetiology thus remains unclear.

Diagnosis

When an oral melanoma is encountered, it is important to exclude the possibility of malignant melanotic lesions elsewhere in the body. Differential diagnosis should include oral melanotic macule, naevus, amalgam tattoo, Kaposi’s sarcoma, smoking-associated melanosis, post-inflammatory pigmentation and melanoacanthoma. Suspicious irregular or heterogenous macules occurring in high risk sites such as the palate and gingiva, should be biopsied as soon as possible. Excisional biopsy can be carried out on lesions of small size, while, incisional biopsy is preferable for lesions that are large and should be performed in the thickest or the darkest area of the lesion, since light areas suggest regression; multiple biopsies should be considered

from heterogenous lesions.

The histologic diagnosis of oral melanoma is easy when the individual tumour cells are found to be melanin-rich, but amelanotic lesions may resemble other neoplasms due largely to the ability of melanoma to adopt a deceptively wide variety of architectural and cytologic patterns. Therefore, the diagnosis is best confirmed by immunohistochemical studies. Stains that have been employed most commonly for the diagnosis of melanoma include S-100, HMB-45, HLA-DR, PCNA and Melan-A, a melanoma-specific marker. It should also be noted that the histologic classification of oral melanoma does not fit well into the categories of the cutaneous counterpart.

Treatment

Due to the rarity of oral melanoma, treatment protocols are scarce and most of the information accrued has been drawn from retrospective review articles. Surgical excision remains the mainstay of treatment and adequate resection may involve approximately a centimetre margin all around the primary tumour, with or without neck dissection. However, anatomical complexities within the region can hamper attempts at complete excision. The presence of regional disease is uncommon and may not influence the therapeutic outcome as significantly as in the cutaneous counterpart. Therapeutic neck lymph node dissections are performed for patients with clinically palpable regional lymph nodes.

Malignant melanoma has been traditionally regarded as a radio-resistant tumour. However, radiation therapy as a primary modality is occasionally used for the elderly and medically compromised, while post-operatively is given as a fractionation regimen for the treatment of selected patients with advanced tumours or where tumour may be either multicentric or the margins may be very close. Preoperative chemotherapy is occasionally used to reduce the size of the melanoma and improve surgical management, while post-operatively, chemotherapy is mainly used in the treatment of disseminated disease and for palliation. Chemotherapeutic agents which are used include dimethyltriazeno imidazole carboxamide, solely or in combination with vincristine and dactinomycin. Immunotherapeutic drugs that are occasionally used include interferon-a, interleukin 2, cimetidine and intralesional lymphokines.

Prognosis-complications-prevention

A system for categorising patients with oral melanoma is in operation and recognises three stages: Stage I, for localised disease, Stage II, when nodal metastases are present, and Stage III, when distant rnetastases are present. Of the patients with oral melanomas, 25% present with nodal involvement and 20% demonstrate clinical or

radiographic evidence of generalised dissemination, most commonly in lung and liver.

The prognosis for patients with oral melanoma remains discouragingly low (5-20%), much lower than that of patients with cutaneous melanoma, since many of these patients are diagnosed at a late stage.

The major factor determining outcome in patients with oral melanoma is the extent of the primary tumour, while tumour thickness greater than 4-5 mm, vascular invasion on light microscopy, and the development of distant metastases, either at presentation or in development during treatment, represent ominous findings, not compatible with prolonged survival. The prognostic value of regional lymph node involvement remains controversial, and whether or not, preexisting melanosis affects the clinical outcome of oral melanomas compared with melanomas presenting de novo is also doubtful.

Indeed, a history of pre-existing melanosis (as long as 10 years), can be found in about one third of all patients with oral melanoma, as the one encountered on the skin, representing the radial growth phase, before the lesion evolves into a vertical infiltrating lesion. Apart from this resemblance, the two entities seem to be biologically and histologically distinct. The oral environment is unique and the abundant blood supply of the oral cavity may facilitates blood vessel invasion and hematogenous dissemination early in the course of the disease. In fact, most commonly, clinical symptoms of oral melanoma are present when significant vertical invasion of the tumour cells into the underlying tissues, including the bone, has already occurred. Finally, early biopsy and close follow-up of any pigmented lesion in the oral cavity secures early diagnosis, simplifies treatment and greatly improves the prognosis.

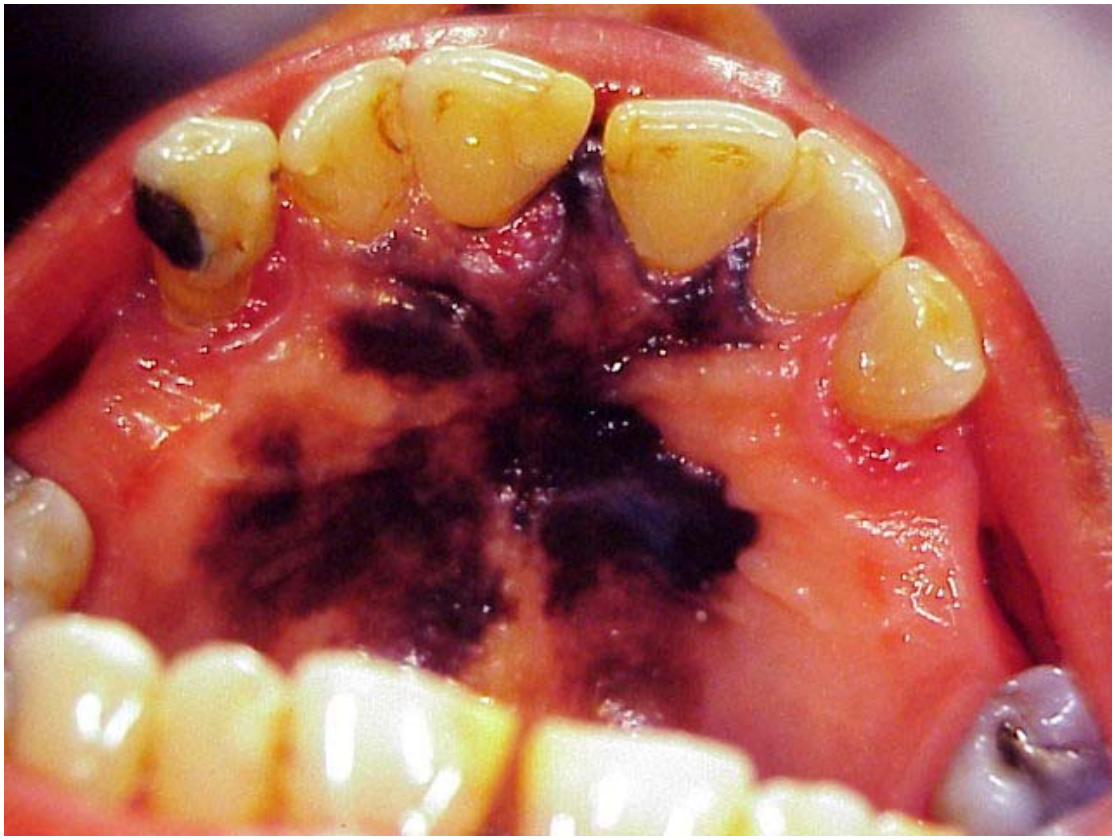

Figure 1. Oral melanoma

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PYOGENIC GRANULOMA

Definition

Pyogenic granuloma (PG) is a common reactive neoformation of the oral cavity, which is composed of granulation tissue and develops in response to local irritation or trauma. Various different names have been given to this entity, reflecting, in part, mistaken concepts about its aetiopathogenesis:

- Botryomycosis hominis
- Botryomycoma
- Telangiectatic granuloma
- Benign pedunculated granuloma
- Pseudobotryomycosis
- Fibroangioma
- Croker and Hartzell disease
- Septic granuloma
- Haemangiomatous granuloma
- Lobular capillary haemangioma
- Eruption capillary haemangioma

The most widely used term is PG, although it does not adequately describe the lesion's characteristics. The term "pyogenic" implies pus production related to an infectious aetiology; however, no pus-producing microorganisms are associated with PG. Moreover, the lesion is not a true "granuloma" (i.e. a specific type of persistent chronic inflammation).

A lesion clinically and microscopically identical to PG may develop from the gingivae of pregnant women. Different names have been used to describe this entity, including pregnancy tumour, epulis, or granuloma, and granuloma gravidarum. Nonetheless, identical cases occur in patients with hormonal changes associated with puberty, menopause, or use of anti-contraceptive medication. Thus, the correct name for this entity is hormonal tumour (HT). Between 0.5% and 5% of pregnant females develop pathological growths in the gums, which are diagnosed as HTs.

Epidemiology

Pyogenic granuloma is a relatively common oral lesion, possibly affecting 1% of the general population with a predilection for the female sex. PGs may occur at any age with a predilection for young adults, most of the patients being in the third or fourth decade of life.

Clinical presentation

The predominant location for PGs is the gingiva, the labial maxillary gingiva being the most frequently affected site, especially anteriorly. Any other oral location may be affected, including the lips, buccal mucosa, and tongue.

PGs present clinically as exophytic, not well-delimited, widely based or pedunculated lesions. The surface is smooth or rough and deep red in colour and the consistency is softer than the rest of the mucosa. Ulceration is a frequent finding, sometimes covered by a fibrinous pseudomembrane, which imparts a whitish appearance. This white necrotic material may resemble pus, but, in the absence of a bacterial infection, no actual pus is produced. Depending on the duration and degree of fibrosis, the lesion may be firmer and paler. The size of PG is usually between 1-3 cm, although much larger lesions are not uncommon.

The majority of PGs are asymptomatic; however, lesions with an intense inflammatory component can be rather painful. Bleeding following mild trauma, or even spontaneously, is frequent. When PGs occur in the gingivae, they are also complicated with specific periodontal alterations (bleeding, periodontal pocket formation, gingival retraction, and tooth mobility).

Aetiopathogenesis

PG is not an infectious but a reactive lesion, due to local irritating factors. Therefore, PG is included in the large group of inflammatory hyperplasias (IHs): neoformations due to increase in the number of constituent cells and not genuine tumours in the sense that their excessive growth is not autonomous but depends on a continuous stimulus of traumatic nature.

The traumatic agents responsible for gingival PG are gingival and periodontal irritants, including plaque accumulation, supra- and infra-gingival calculus, overhanging margins of crowns and fillings, implantation of foreign material etc. Other traumatic agents, such as biting, are responsible for PG developing in other parts of the mouth. Healing extraction sites may also give rise to a PG, sometimes termed epulis granulomatosa. Independent of their exact nature, the various chronic traumatic insults induce inflammation, followed by repair with production of excessive granulation tissue.

Some investigators have related PG to prolonged treatment such as with cortisone, oral contraceptives, and diabetic medications, or even with allogeneic bone marrow transplantation.

HT is associated with hormonal changes, most often associated with pregnancy, but also occurring with puberty, menopause, or contraceptive treatment. The increase of oestrogens and progesterone produces an increase in vascularisation, capillary

proliferation, and vascular permeability. These changes lead to a greater susceptibility of the gums against local irritants, such as abundant plaque and calculus, therefore rendering the patients prone to inflammatory and reactive processes, including HT.

Diagnosis

A definitive diagnosis of PG is reached through evaluation of clinical and histopathological characteristics. Microscopically, PGs appear covered by a stratified squamous epithelium, which is atrophic or ulcerated in almost 100% of cases. Ulceration is common. The underlying connective tissue is oedematous and occupied by exuberant granulation tissue featuring a large proliferation of small capillaries. A mixed inflammatory infiltrate, mainly composed of polymorphonuclear leukocytes, and to a lesser extent, lymphocytes, is evident. These pathological characteristics, along with the clinical features, make these lesions very similar to exophytic capillary haemangiomas. For this reason, on occasions, it is convenient to perform an aspiration puncture with a fine needle before extirpation to confirm the clinical impression of a vascular lesion and to avoid problems of haemorrhage.

The degree of fibrosis is minimal, although older lesions become progressively more fibrosed. In untreated, chronically irritated lesions, there is a progressive maturation of the lesion with gradual replacement by collagenous, fibrous connective tissue. The final stages of a PG may be identical to a fibrous hyperplasia.

PG in a gingival location should be differentiated from other reactive gingival lesions, such as peripheral giant cell granuloma (PGCG) and peripheral ossifying fibroma (POF). Although clinical differences from typical PG do exist (e.g. PGCG is usually associated with bluish-purple hue and may cause a “cupping” resorption of the underlying bone, while POF is pinker and often non-ulcerated), the final diagnosis relies on histopathological examination of the excised specimen.

Treatment

Surgical excision of PGs is the treatment of choice. Excision should also include removal of the base of the lesion, with extension down to periosteum, and curettage. Extraction of associated teeth is rarely necessary. In small incipient lesions, extirpation of the lesion and electric-coagulation of the base is recommended. Nowadays, the use of different types of LASER extirpation is available and particularly useful for control of bleeding in PGs and other haemorrhagic lesions.

Elimination of the responsible chronic irritating factor is always of paramount importance. Hence, the suggested protocol of action for PG includes initial elimination of the traumatic factors with subsequent surgical excision. If the lesion is small, reddish

and free of fibrosis, the elimination of the traumatic factors may be sufficient for its own self extinction. Even if total resolution is not achieved, PG will likely lose its inflammatory and granulation tissue component, thus being smaller, less haemorrhagic and less prone to surgical complications.

Because of the risk of complications and a higher risk of recurrence for HT removed during pregnancy, surgical excision should be deferred with the exception of cases featuring excessive haemorrhage and ulceration, or marked functional and aesthetic problems. If surgery is necessary, it is preferably done after the second trimester and, due to the high content of vascular tissue, LASER treatment is advisable.

All obtained specimens should be evaluated microscopically to confirm the diagnosis.

Prognosis and complication

Elimination of the causative traumatic factors followed by complete surgical excision of the lesion constitutes the basis for definitive treatment and prevention of recurrences. However, according to some authors, recurrences occur in almost 20% of cases. During surgical removal, special attention should be paid to complete removal of the base of the lesion to avoid possible recurrences.

Complications of treatment include haemorrhage, which can be prevented through previous reduction of the amount of inflamed granulation tissue by means of elimination of the irritating factors. Use of LASER allows control of haemorrhage through induction of coagulation. On the other hand, extirpation of anterior large lesions can produce a wide range of gingival defects, which pose important aesthetic problems. In these cases, a more laborious and meticulous surgical approach will contribute to a cosmetically-acceptable result.

There is a general consensus that HT regresses after childbirth, although it rarely disappears completely. In our experience, the HTs persisted one month after childbirth, although smaller in size. Surgical excision and periodontal management were carried out without subsequent recurrences.

Prevention

Prevention of recurrent or newly-developed lesions of PG entails complete removal of the causative traumatic insult. For gingival lesions, implementation of meticulous oral hygiene is of paramount significance. In cases that dental restorations and appliances, or tooth and periodontal abnormalities are implicated, these factors should be corrected or eliminated.

The adoption of preventive measures during pregnancy, such as better oral hygiene, will reduce the risk of pregnancy-associated HT.

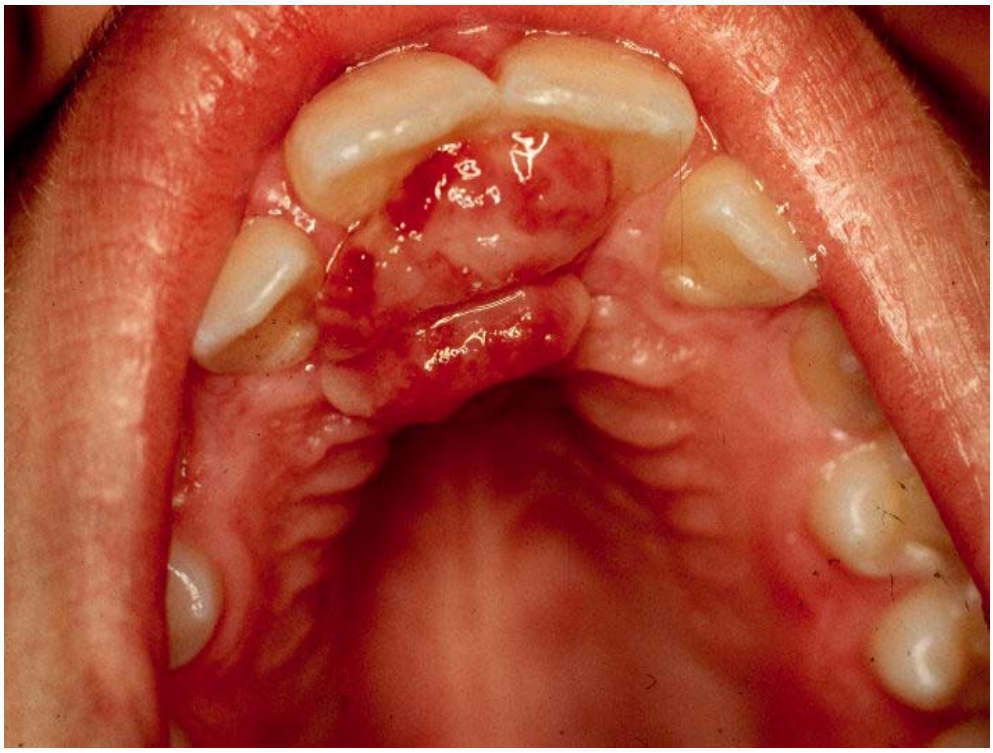

Figure 1. Pyogenic granuloma (clinical)

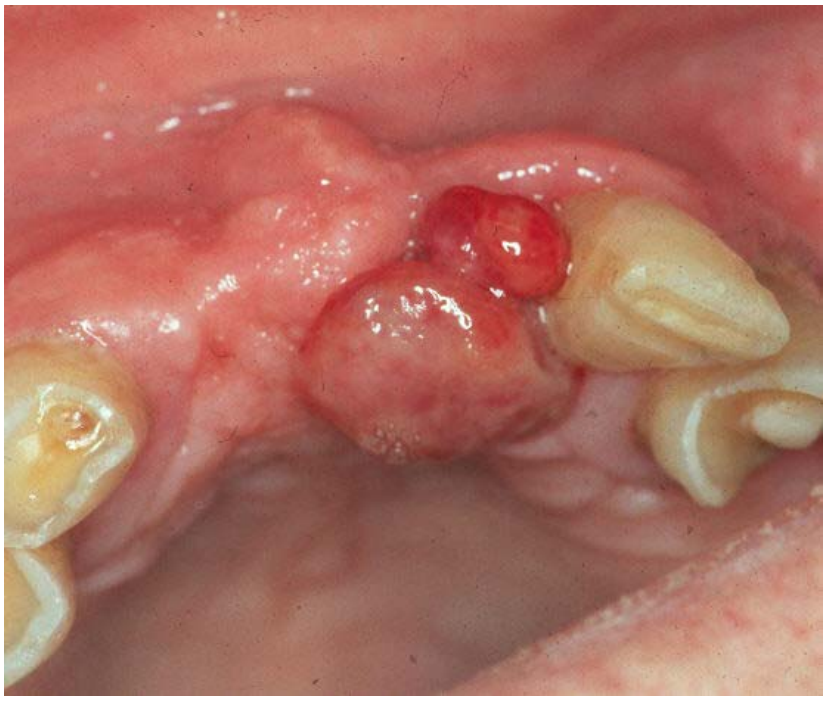

Figure 2. Pyogenic granuloma (clinical)

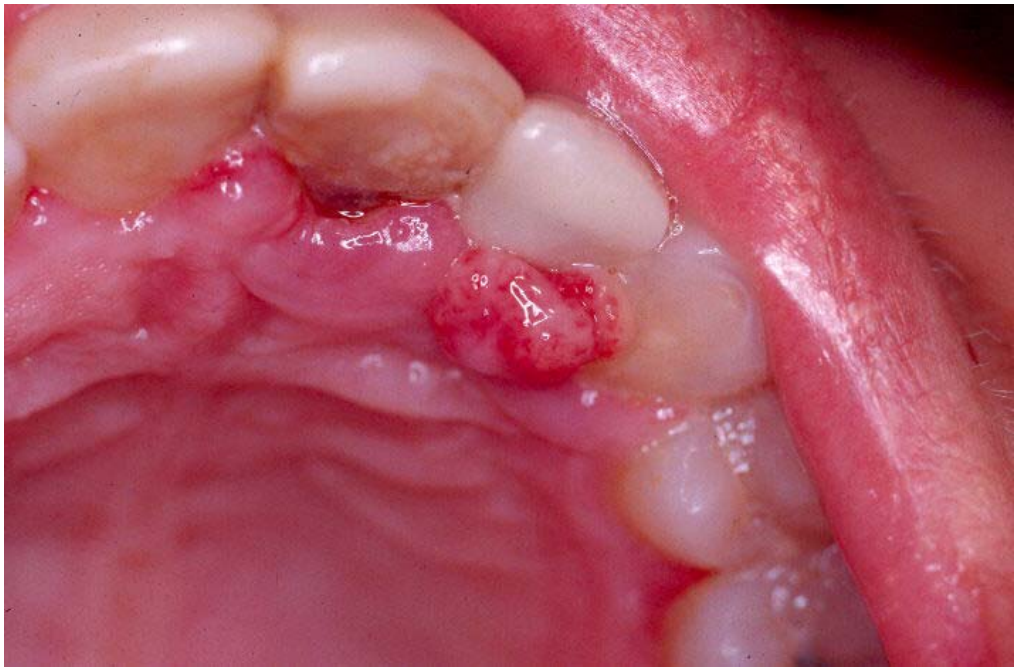

Figure 3. Hormonal tumor (clinical)

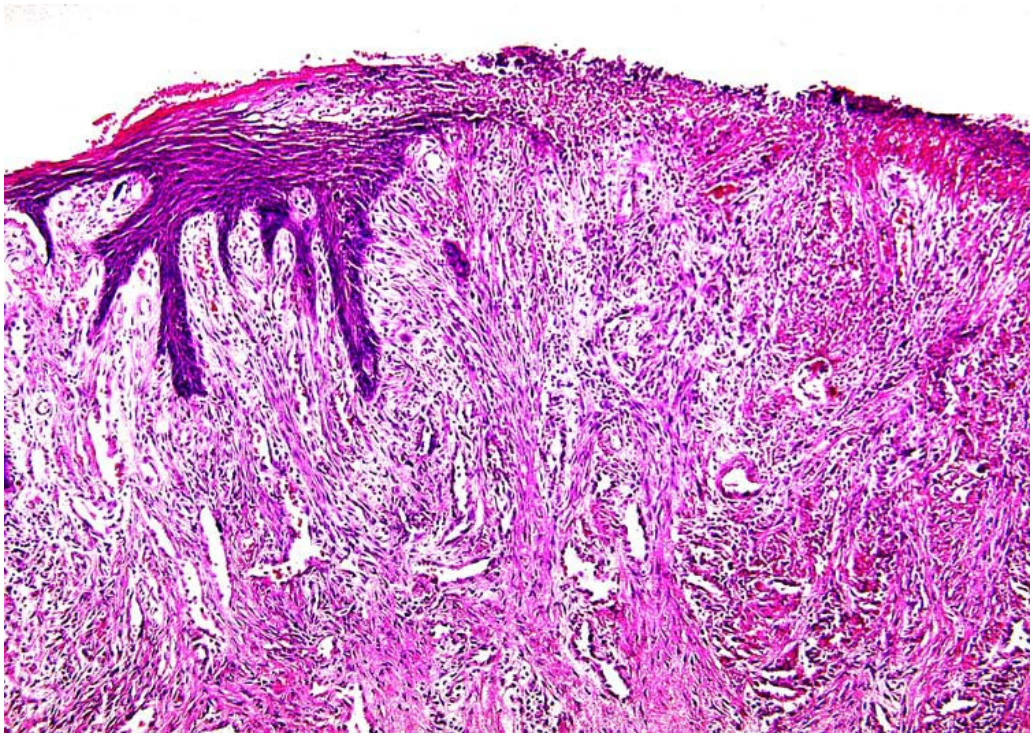

Figure 4. Pyogenic granuloma (histopathological, H & E 100x)

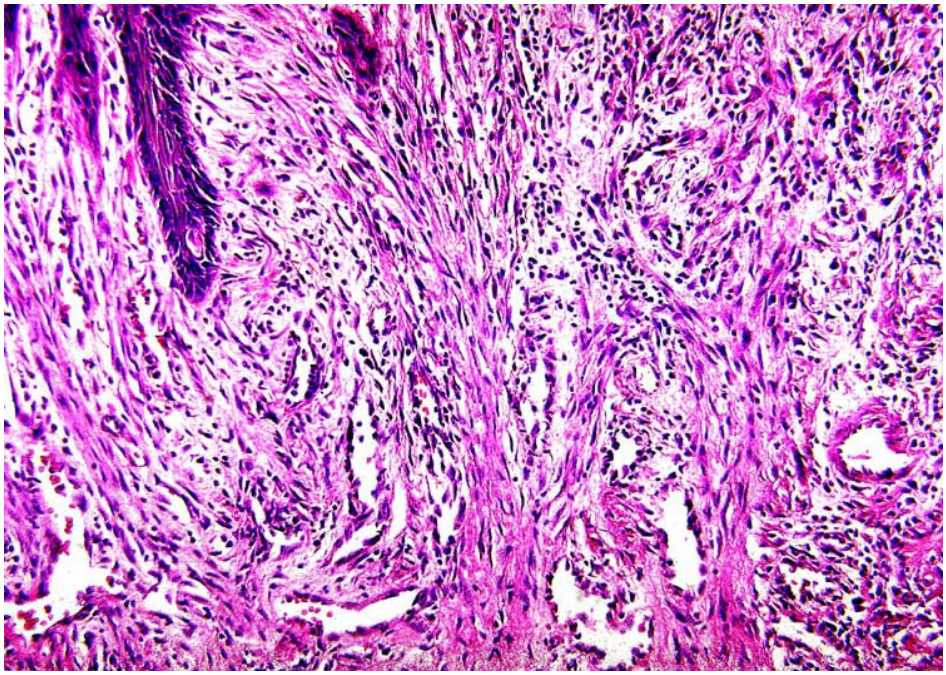

Figure 5. Pyogenic granuloma (histopathological, H & E 200x)

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SJÖGREN'S SYNDROME

Definition

Sjögren's syndrome is a systemic autoimmune disease characterised by dry mouth and dry eyes and various autoimmune changes, confirmed by a blood test or salivary gland biopsy. Sjögren's syndrome can occur as an independent, primary condition, "Primary Sjögren's syndrome", or accompany another autoimmune disease, such as rheumatoid arthritis, in which case it is known as Secondary Sjögren's syndrome. In addition to 1) dryness of the mucous membranes and skin, Sjögren's syndrome can also lead to 2) general symptoms such as fatigue, musculoskeletal pain and less commonly 3) pathological changes in internal organs and 4) various complications such as caries, candidosis, congenital heart block and lymphoma.

Epidemiology

Sjögren's syndrome is considered to be one of the commonest autoimmune diseases but there is no consensus as to how many sufferers there are worldwide. One of the problems, in estimating exact numbers, is that many different criteria have been used to diagnose Sjögren's syndrome at different times and in different countries. In addition, many sufferers probably do not seek professional advice about their condition or it is not recognised by health care professionals. It has been reported that Sjögren's syndrome affects between 0.04-4.8% of the population and this includes patients with rheumatoid arthritis, one third of whom develop the secondary form. Sjögren's syndrome is much more common in women (only 1 in 10 are men) and usually presents between the ages of 40 and 60 years.

Clinical presentation

The most common symptoms of patients with Sjögren's syndrome relate to dryness of the eyes and/or mouth. Saliva lubricates the mouth and has an important role in protecting against candidal infections (thrush) and dental caries (decay). As the salivary glands are directly involved in Sjögren's syndrome, they may become swollen or develop infections. Patients with a reduced flow of saliva frequently complain of difficulty or soreness when eating and/or speaking and notice that their taste is affected. Swallowing may be difficult and frequent sips of water are often required; occasionally there is hoarseness of the voice. Dryness of the eyes can result in a feeling of "irritable" or "gritty eyes" and strong lights may cause discomfort. An accumulation of mucous or debris can result in "sticky" eyes and recurrent eye infections. Dryness may also affect other sites in the body, such as the skin, and vaginal dryness can result in painful or difficult sexual intercourse. All these problems can severely compromise a patient's quality of life. Another common complaint of patients with Sjögren's syndrome is feeling more tired than usual and this lethargy may prompt patients to seek medical advice. Sjögren's syndrome is also characterised by joint (and muscle) pain, which is known as arthralgia (and myalgia), typically affecting the hand,

wrist and foot joints but with no accompanying swelling. The third most common general symptom of Sjögren's syndrome is Raynaud's phenomenon, in which the fingers feel cold and turn white. Occasionally patients with Sjögren's syndrome seek medical attention because of other symptoms resulting from involvement of the skin, thyroid gland, stomach, bowel, liver, lungs, kidneys and bladder. Other organs, such as the nervous system, are probably less commonly involved. Sjögren's syndrome may also have haematological manifestations which may be diagnosed when routine blood tests are carried out and reveal changes such as anaemia or raised erythrocyte sedimentation rate (inflammatory marker in the blood), which prompt further investigation.

Etiopathogenesis

The exact cause of Sjögren's syndrome is unknown. The consensus opinion at the present time is that an environmental factor, such as a yet unknown virus, triggers an abnormal immune reaction. In Sjögren's syndrome, as in other autoimmune disorders the body reacts against itself, with an exaggerated immunological response, which appears to affect regulatory molecules in cells and tissues. This inappropriate response can lead to an accumulation of inflammatory cells in the salivary or tear (lacrimal) glands and the production of autoantibodies, which can be demonstrated in a blood sample. The mechanism, by which the function of glands is reduced has yet to be worked out. Although Sjögren's syndrome is not uncommon, relatively few people develop the disease and it is therefore likely that those affected have an inherent genetic susceptibility. It is rare, however, for Sjögren's syndrome to be passed from mother to daughter, and familial cases are the subject of ongoing investigations. The female preponderance of Sjögren's syndrome, particularly in the mature women, suggests that a gender-linked susceptibility – possibly related to diminished or altered production of sex hormones may be involved.

Diagnosis

The European-American consensus criteria for the diagnosis of Sjögren's syndrome have now been agreed and are presented in Table 1. It should be emphasised that the symptoms and clinical findings do not appear overnight and that a definite diagnosis of Sjögren's according to these criteria is not necessary for treatment of troublesome symptoms and complications.

<u>Sicca syndrome</u>

A diagnosis of this is sometimes given to patients who have dryness of their eyes and/or mouth but do not have the objective signs or immunological markers necessary for the diagnosis of Sjögren's syndrome. Sicca means dry(ness) and may be a result of other illnesses (e.g. depression) affecting the functioning of glands and radiotherapy for cancer, or the treatment of thyroid disease. A large number of drugs (e.g. antidepressants) can cause sicca symptoms. Symptomatic treatment for sicca symptoms is similar to that available for Sjögren's syndrome.

Treatment

At the present time, there is no curative treatment for Sjögren's syndrome, but symptoms and complications can be effectively managed by the local (topical) therapy and/or drugs taken systemically. Dryness of the mouth and eyes can be managed by either stimulating the existing function of the saliva or tear producing glands or by providing substitute secretions, e.g. saliva or artificial tears. Some of the locally used drugs contain active substances, like mucolytic or anti-inflammatory agents, vitamin A, topical estrogens etc. The severity of disease, degree of organ involvement and type of symptoms together with the preference of patients will dictate the management of Sjögren's syndrome.

Dry Mouth

- Stimulate salivary gland function by regularly chewing sugar-free gum, sweets or pastilles.
- Sip water or suck ice cubes.
- Use artificial saliva or replacement gels as required.
- Candida (thrush infection) in the mouth should be promptly treated.
- Visit your dentist regularly and seek advice on appropriate diet (for example avoid sweet foods) and the maintenance of good dental hygiene. Fluoride supplements and chlorhexidine may be indicated.
- The use of a systemic drug known as a "secretagogue", e.g. pilocarpine or cevimeline, which stimulates any residual glandular function may be indicated, if topical therapy is not effective for dry mouth (or eyes).

Dry Eyes

- Seek professional advice concerning the use of tear substitutes (eye drops, gels and ointments).
- Artificial tears should be preservative free, particularly if used on a frequent basis.
- Mucolytic drops such as acetylcysteine may be helpful if mucous threads ("sticky eyes") are a problem.
- Pilocarpine or cevimeline may be beneficial (see above).
- Consider use of moisture-retaining spectacles, e.g. swimming goggles and room humidifiers.
- Conservation of tears by blocking their natural drainage may be indicated. Temporary punctal plugs are inserted and if beneficial the tear ducts (canaliculi) can be surgically closed.

Dryness in Other Sites

- Vaginal dryness – use moisturising gels or pessaries for lubrication, particularly if intercourse is difficult or painful. Occasionally, topical or systemic hormone replacement can be helpful.
- Ask your doctor, or pharmacist, for advice about managing dryness of other mucous membranes, e.g. the throat.
- Use moisturising creams and emollients for dryness of the skin and lips.
- Avoid dry, smoke-filled environments.

General Manifestations of SS

- Excessive fatigue should be investigated to eliminate other systemic causes (e.g. anaemia or thyroid disease).
- Joint and muscle pain can be treated symptomatically with analgesics (pain killers), such as paracetamol (acetoaminophen) or a non-steroidal anti-inflammatory drug.
- For severe joint pain or extreme fatigue, your doctor may recommend hydroxychloroquine, or less commonly, a glucocorticosteroid.
- White fingers (Raynaud's phenomenon) may respond to a vasodilator drug, which is usually a calcium blocking agent.
- Drugs which directly affect the immune system, (known as "immunomodulatory" drugs), may be considered in cases where there is significant organ involvement. Drugs, such as methotrexate, azathioprine or ciclosporin have potentially serious side effects which must be considered when assessing their potential benefits for Sjögren's syndrome.
- Effective management sometimes necessitates replacement therapy, e.g. thyroid hormone in hypothyroidism and vitamin B12 in chronic atrophic gastritis. In primary biliary cirrhosis, non-irritating bile acid ursodeoxycholic acid is used to substitute for irritating endogenous bile acids and in interstitial cystitis the defective, protective, layer of the urinary bladder can be replaced by proteoglycans. Renal tubular acidosis can be treated with sodium bicarbonate and diuretic drugs which diminish calcium secretion and reduce the risk of developing kidney stones. (582 words)

Prognosis and Complications

Sjögren's syndrome is a chronic disease which usually runs in cycles and does not usually lead to serious incapacity or invalidity. Patients with Sjögren's syndrome may, however, have a diminished quality of life because of mucosal dryness, fatigue and aching muscles and joints. Occasionally patients with Sjögren's syndrome become depressed, but this tends to be a feature of many other chronic illnesses as well. One of the most distressing and frustrating aspects of Sjögren's syndrome for patients is that the diagnosis of their disease may be delayed for up to ten years from the onset of symptoms. Due to the rather diverse nature of symptoms in Sjögren's syndrome, patients may present to a wide range of differing specialties (including oral medicine/surgery, rheumatology, ophthalmology and ENT specialists) and may not be diagnosed during the early stages of the disease. It is, therefore, important that the health care professionals and the general public are aware of this condition which should be suspected if anyone complains of a persistently dry mouth and/or eyes. Most complications of Sjögren's syndrome can be prevented or managed by early institution of local and systemic (if appropriate) treatment. Early recognition of rampant caries (dental decay) is important to prevent long-term damage to the teeth and avoid the provision of dental prostheses (false teeth). Recurrent oral candidosis (thrush infection) can be treated by local or systemic antifungal medication. Dryness of the eyes, if appropriately treated by the use of

artificial tear substitutes or punctal occlusion, rarely leads to permanent scarring of the ocular surfaces or ulceration of the cornea. Severe joint injury and destruction are rare in Sjögren's syndrome except for those secondary cases which are associated with rheumatoid arthritis. If involvement of internal organs is detected early, serious complications are uncommon.
There are two specific complications of Sjögren's syndrome that merit special consideration, one is a significant but small risk of developing lymphoma and the other is a potential but small risk of heart block in babies born to mothers with Primary Sjögren's syndrome. Although the risk for lymphoma has been estimated to be over 40 times higher in Sjögren's syndrome than the general population the actual risk is still modest. Lymphoma is a malignancy occurring in the lymph nodes or collections of lymphoid tissue elsewhere in the body. Lymphomas may arise in the salivary glands of patients with Sjögren's syndrome and are known as "MALTomas" (from the mucosal associated lymphoid tissue). If patients develop persistently enlarged salivary glands, particularly if the parotids significantly increase in size, then a more detailed examination of the glands is required (e.g. ultrasound, CT scan or MRI examination and biopsy – usually a fine needle aspiration). Other systemic features such as slight fever, unexplained weight loss and progressive fatigue should be investigated; there may also be a change in the immunological markers in the blood. It is important to emphasise that the risk of developing lymphoma in Sjögren's syndrome is still extremely low and some types of lymphomas, e.g. gastric lymphoma, can be treated with simple eradication of Helicobacter pylori.
It is thought that the rare complication of congenital lupus skin eruption and heart block in the unborn or new born children of patients with Sjögren's syndrome is the result of maternal antibodies crossing the placenta. However, currently the exact identity and mechanism of action of these antibodies is unknown. Irrespective of the mechanism it is known that the development of the conduction system within the heart is disturbed and the baby may be born with heart block, which may require a pacemaker at birth. For this reason, women suffering from Sjögren's syndrome should be carefully monitored during pregnancy and monitored in hospital units with paediatric expertise in preventing, diagnosing and treating intrauterine or neonatal heart disturbances.

Prevention

In the light of current knowledge the cause of Sjögren's syndrome remains unknown and therefore prevention is not possible. Many of the complications of Sjögren's syndrome may however be prevented or symptoms satisfactorily controlled by the strategies already discussed. Early recognition is the key to preventing many of the long-term complications of Sjögren's syndrome and it is important that patients with multi-system involvement are treated by a team of health care professionals. Hypothyroidism, interstitial pneumonias, celiac disease and chronic atrophic gastritis are relatively common in Sjögren's syndrome and can, when suspected, be easily diagnosed and treated before any permanent changes result.

Patients with Sjögren’s syndrome, like the rest of the population, should strive to maintain a healthy lifestyle with a balanced diet and regular exercise; tobacco smoking and excessive alcohol consumption are best avoided.

Many European countries now have patient support groups for patients with Sjögren’s syndrome; these provide mutual support and helpful advice for coping with symptoms and improving quality of life.

Table 1. Revised international classification criteria for Sjõgren's syndrome
(Vitali C, Bombardieri S, Jonson R et al (2002). Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group)

I Ocular symptoms: a positive response to at least one of the following questions:

1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
2. Do you have a recurrent sensation of sand or gravel in the eyes?
3. Do you use tear substitutes more than 3 times a day?

II Oral symptoms: a positive response to at least one of the following questions:

1. Have you had a daily feeling of dry mouth for more than 3 months?
2. Have you had recurrently or persistently swollen salivary glands as an adult?
3. Do you frequently drink liquids to aid in swallowing dry food?

III Ocular signs: that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:

1. Schirmer's test performed without anaesthesia (≤ 5mm in 5 minutes).
2. Rose bengal score or other ocular dye score (≥4 according to van Bijsterveld's scoring system).

IV Histopathology: in minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialadenitis, evaluated by an expert histopathologist, with a focus score ≥1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm^2 of glandular tissue.

V Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:

1. Unstimulated whole salivary flow (≤1.5 ml in 15 minutes).
2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of obstruction in the major ducts.
3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer.

VI Autoantibodies: presence in the serum of the following autoantibodies:

1. Antibodies to Ro (SS-A) or La (SS-B) antigens, or both.

For the diagnosis of Primary SS:

In patients without any potentially associated disease, primary SS may be defined as follows:

a. The presence of any 4 of the 6 items is indicative of primary SS, as long as either item IV (Histopathology) or VI (Serology) is positive.
b. The presence of any 3 of the 4 objective criteria items (that, is items III, IV, V, VI).
c. The classification tree procedure represents a valid alternative method of classification, although it should be more properly used in clinical-epidemiological survey.

For the diagnosis of Secondary SS:

In patients with a potentially associated disease (for instance, another well defined connective tissue disease), the presence of item I or item II plus any 2 from among items III, IV and V may be considered as indicative of secondary SS.

Exclusion criteria:

Past head and neck radiation treatment

Hepatitis C infection

Acquired immunodeficiency disease (AIDS)

Pre-existing lymphoma

Sarcoidosis

Graft versus host disease

Use of anticholinergic drugs (since a time shorter than 3-fold the half life of the drug).

Additional information about investigations

1 Schirmer's test: a small piece of blotting paper is inserted into the eye to measure tear production.

2 Rose Bengal test: an eye specialist will place eye drops containing dye (e.g. Rose Bengal or Lissamine green) and examine the surface of the eye, using an instrument called a "slit-lamp".

3 Lip biopsy: a small (minor) salivary gland can be surgically removed from inside the lower lip, under local anaesthesia. This is examined under a microscope to look for changes suggestive of Sjögren's syndrome.

4 Assessment of salivary gland function: this includes measurement of saliva flow (e.g. by spitting into a container) or injecting a labelled substance (isotope) into a vein or contrast dye into the salivary gland ducts which empty into the mouth. (689 words)

Pictures

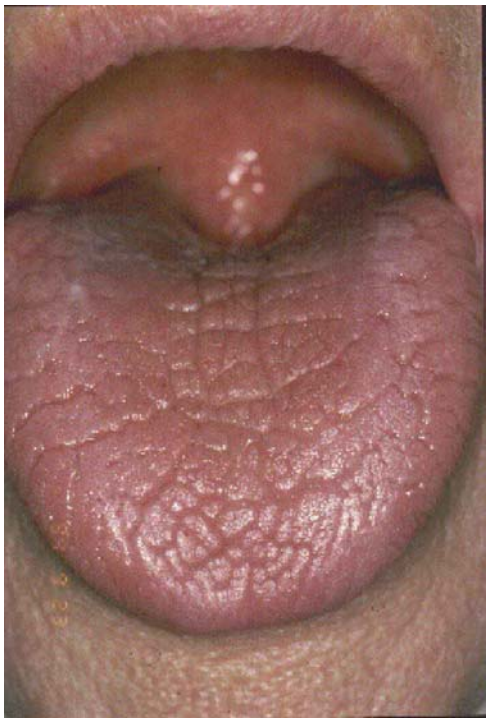

Figure 1. Dry lobulated tongue

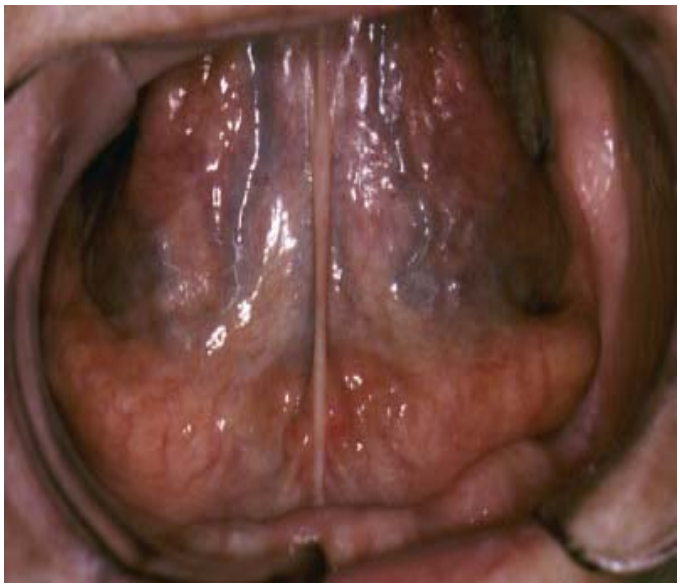

Figure 2. No pooling of saliva on the floor of the mouth

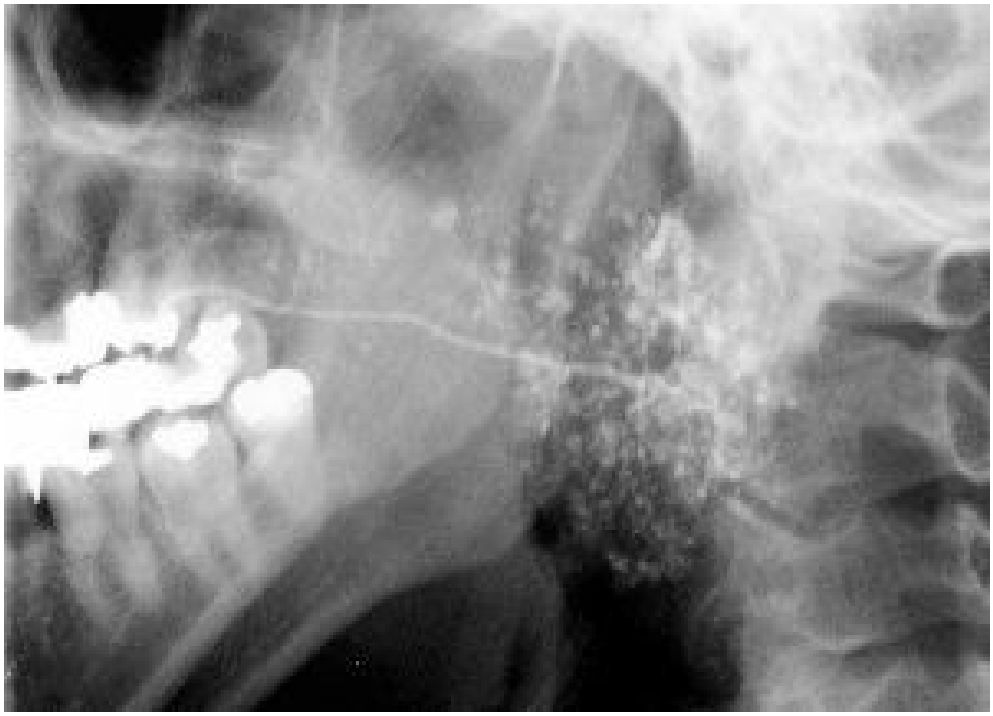

Figure 3. Primary Sjögren's syndrome: sialography

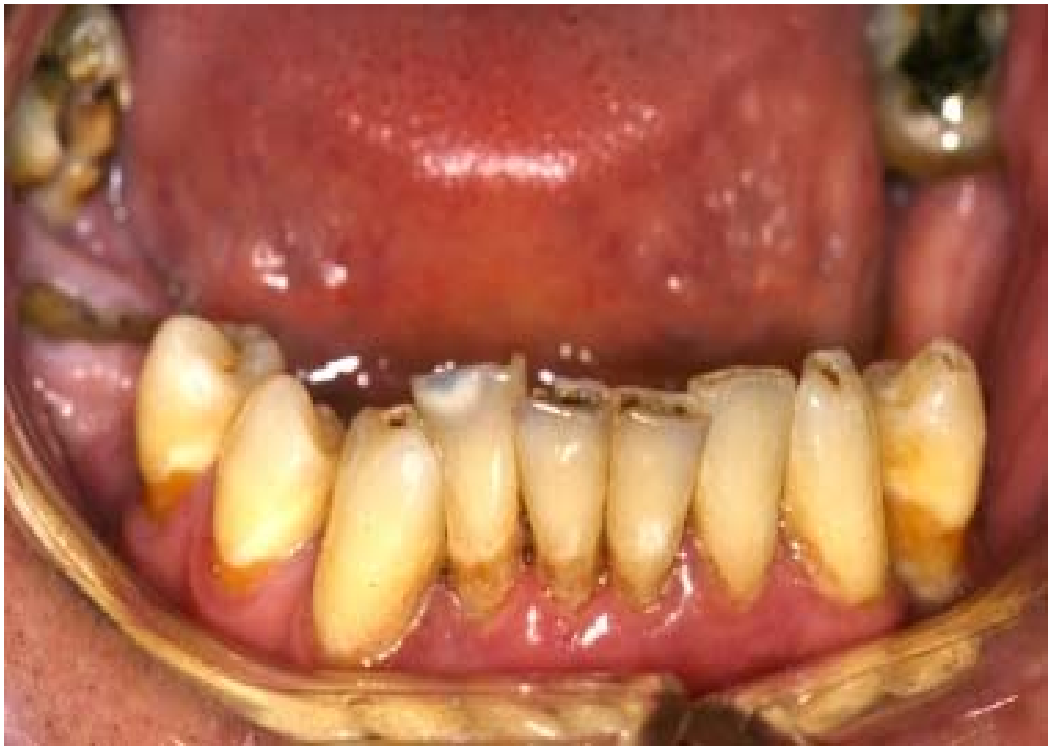

Figure 4. Primary Sjögren's syndrome: dental decay

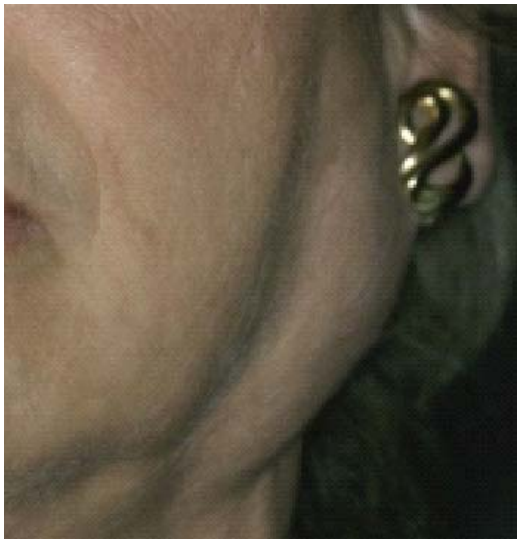

Figure 5. Primary Sjögren's syndrome: parotid gland swelling

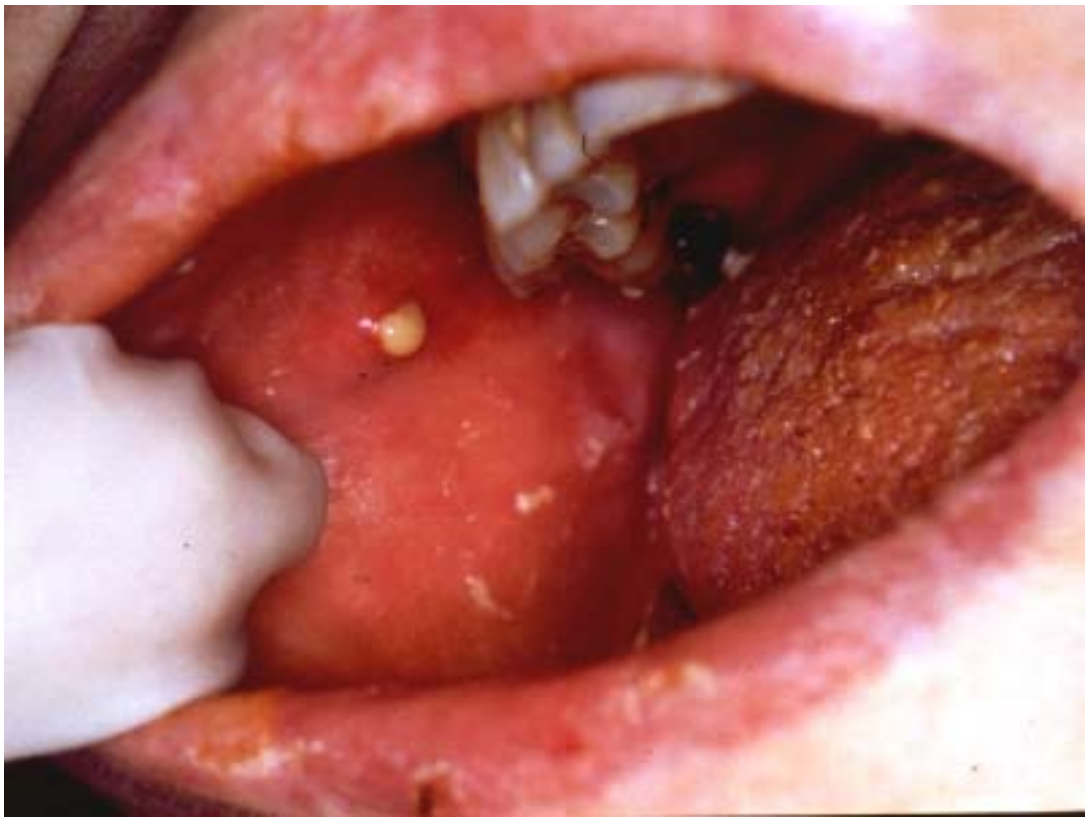

Figure 6. Primary Sjögren's syndrome: infected parotid gland –pus from duct

Further reading

1 Vitali C, Bombardieri S et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002; 61:554-8

2 Sjögren's syndrome. A concise guide to diagnosis and management for health professionals. The British Sjögren's syndrome Association.

3 Jonsson R, Haga H-J, Gordon T: Sjögren's syndrome. In: Arthritis and Allied Conditions – A Textbook of Rheumatology, Koopman WJ , ed 14th Edition. Lippincott Williams & Wilkins, Philadelphia, 2001, pp 1736-1759.

Links

Sjögren's syndrome Foundation www.sjogrens.org/

British Sjögren's Syndrome Ass. http://ourworld.compuserve.com/homepages/bssassociation

EFFECTS OF TOBACCO ON ORAL HEALTH

Definition

Tobacco is consumed in a variety of different ways, though smoking of manufactured cigarettes is the most prevalent form of its use. The emergence of widespread cigar use particularly among adolescents of both sexes has been reported in the past decade in the US. Cigars have higher total nicotine content than cigarettes do and can deliver nicotine both through smoke and through direct oral contact with the tobacco wrapper. Cheroots are small cigars made of heavy bodied tobacco. Bidi smoking is a popular form of tobacco use in south Asia, accounting for one-third of the tobacco produced in India for smoking. Bidis and kreteks are gaining popularity among young people in North America, and more than 15% of adolescent smokers use these tobacco products. Pipe smoking is one of the oldest methods of smoking and was brought to Europe by sailors from Americas. Water pipes include special receptacles through which smoke has to pass, ostensibly to reduce its harmful effects. Hookah is an Indian water pipe. The habit of reverse smoking by holding the glowing end of cigarettes or cigars within the oral cavity is described in parts of India, south America and the Philippines. The habit is practiced extensively by older women living in rural areas.

Smoked tobacco

Tobacco smoke is made up of “side-stream smoke” from the burning tip of the cigarette and “main-stream smoke” from the filter or mouth end.

Tobacco smoke contains thousands of different chemicals which are released as particles and gases. Many toxins are present in tobacco smoke. The particulate phase includes nicotine, "tar" (itself composed of many chemicals), benzene and benzo(a)pyrene. The gas phase includes carbon monoxide, ammonia, dimethylnitrosamine, formaldehyde, hydrogen cyanide and acrolein. Some of these have marked irritant properties and some 60, including benzo(a)pyrene and dimethylnitrosamine, have been shown to cause cancer.

The tar yield of different brands of cigarettes range from 0.5 mg to 26 mg (averaging 12.5 mg.), with the most popular brands containing 15-17 mg of tar. In the European Union (EU) cigarettes have to contain less than 12 mg of tar from 1998. Nicotine yields range from 0.05 mg to 1.7 mg, with the most popular brands yielding 1.0 mg of nicotine. In developed countries over 95% of manufactured cigarettes consumed are filter-tipped.

About 10% consume tobacco as roll-your-own cigarettes mostly among lower socioeconomic groups.

Smokeless (chewing) tobacco (ST)

There are two main types of smokeless tobacco - chewing tobacco and snuff. The most written about is smokeless tobacco use among Asians taken with betel/areca quid. Over 90 percent of Indians add tobacco to the betel quid mixture. Commercially prepared betel quid products that contain mostly areca nut and flakes of tobacco are called gutka. Other ST products which carry significant mutagenicity are toombak used in the Sudan, shamma in the Jizan province in Saudi Arabia, powdered tobacco and alkali mixtures such as nass/naswar used in northern and central Asia and in Pakistan, khaini (a mixture of ST and lime) used in Bihar state of India and Nepal, and boiled/sweetened ST called zarda mostly used by people from Bangladesh. All these forms of tobacco use are associated with an increased risk of oral cancer.

Second-hand or environmental tobacco smoke (ETS)

ETS is carcinogenic to human beings. Meta-analyses show that there is a significant association between lung cancer and smoke exposure from a spouse and also between lung cancer and exposure at work. Risks for other cancer types are inconclusive. There is at present insufficient evidence that children exposed to parental smoke have an altered risk of developing any cancer.

Epidemiology

Tobacco, which annually kills 4.9 million people worldwide at present, is estimated to take 10 million lives every year by 2020. The more depressing part is that half of them will die in their middle age. Global estimates of smoking prevalence by each country is given in a WHO data base for reference. These are based on adult and youth smoking behaviours collected from population-based, cross sectional surveys at a given point of time. China is the largest producer of tobacco in the world as well as the largest consumer. A national prevalence survey in 1996 among adults (age 15+) found that 63% of males smoked.

National surveys of persons aged 18 and older from 1970 onwards report a decline in prevalence in USA and most western European countries. The rate of decline among women is less than for men, and the quit index for men is substantially higher than for women. Fig 1 illustrates trends in the USA, UK and Japan over five decades. Both in UK and USA there are now twice as many former cigarette smokers as current smokers. In

general the prevalence of smoking in most population groups is lowest among those with the highest educational level. By race, smoking among adult blacks is similar to whites in most countries. Denmark has the highest rates of smoking in the EU.

Clinical presentation

General effects

Smoking-attributed diseases include cancer of trachea, lung, bronchus, lip, mouth and pharynx, ischemic heart disease, stroke, hypertension, bronchitis, chronic obstructive pulmonary disease, emphysema and asthma. Due to substantial decrease in smoking in countries such as the UK male lung cancer rates have decreased rapidly in the last decade. On current trends, the annual number of smoking-attributable deaths among women should exceed that for men shortly after the year 2000.

Effects of tobacco on teeth and oral health

The damaging and harmful effects of tobacco usage on oral health are now well recognized, in particular a higher prevalence and severity of periodontal diseases among smokers and the association of tobacco use with candidosis, and with oral malignancies. Several recent documents have reviewed the scientific evidence relating to the oral disease burden attributable to tobacco use and have highlighted the role and the need for the dental profession to get involved with tobacco intervention.

Smoking causes discolouration of teeth and some argue that tobacco in fact might increase dental decay as it lowers salivary pH and the buffering power. Smoking is likely to cause halitosis and may affect smell and taste. Smokers may present with generalised melanosis of the oral mucosa (Fig 2) that often necessitate investigations to exclude other systemic disorders. Wound healing is impaired in tobacco smokers possibly due to local vasoconstriction and poor neutrophil function. There is fair evidence that tobacco use is a major factor in the progression of periodontal disease. Smokers have an increased prevalence of periodontitis, and their disease severity is higher with greater alveolar bone loss resulting in deeper pockets compared with non smokers. Acute necrotising ulcerative gingivitis (ANUG) (Fig 3) has been shown to be associated with heavy smoking. Periodontal therapy often fails among smokers and it is difficult to halt attachment loss. Possibly for similar reasons dental implant failure is more common in smoking subjects compared with non smokers.

Oral cancer

Oral squamous cell carcinoma presents in a variety of ways such as white and red patches, non-healing ulcers or exophytic growths. Most early lesions are asymptomatic. Persistent ulceration with rolled margins and fixation to underlying tissues are pathognomonic signs of oral malignancy (Fig 4). In late stages disease spreads to adjacent structures notably involving regional lymph nodes, and can cause mobile teeth and loss of teeth or even pathological mandibular fractures. These stages may be associated with pain, numbness or paraesthesia. The clinical features of oral cancer are described elsewhere. Currently diagnosing oral cancer relies on pathological examination by biopsy and use of imaging techniques to estimate the spread of the disease. Over 80 percent of oral cancers are associated with tobacco use.

Oral leukoplakia

Oral leukoplakia is the most common potentially malignant lesion defined as a predominantly white lesion of oral mucosa that cannot be characterised as any other definable lesion. The appearance of leukoplakia varies from uniformly white homogeneous lesions (Fig 5) to non-homogeneous speckled lesions with red and/or nodular features (Fig 6). Leukoplakia is often associated with tobacco use though idiopathic forms of leukoplakia are recognised. The site of the oral cavity affected by leukoplakia is often said to be associated with the type of tobacco habit practiced; lateral tongue and floor of mouth in cigarette smokers, palate in pipe smokers and reverse smokers, commissures in bidi smokers, buccal groves in tobacco chewers where they park the quid and lower or upper labial mucosa in snuff dippers. In a recent study in the Netherlands 64% of men and 60% of women with oral leukoplakia were smokers. Tobacco use in men was significantly associated with leukoplakia of buccal mucosa and with all leukoplakia of floor of mouth in both sexes (6). Oral leukoplakia in smokers need to be investigated by biopsy to assess any dysplasia. Moderate to severe oral epithelial dysplasia (Fig 7) when present necessitate surgical intervention. Intervention studies have demonstrated that leukoplakia present in smokers might be reversible when smoking habit was reduced or given up.

Erythroplakia

Tobacco may underlie some cases of erythroplakia.

Smoker's palate (Leukokeratosis nicotina palati)

A greyish white discolouration of the palate with multiple red elevated dots (inflamed minor salivary gland openings) is often encountered in chronic smokers. This is

considered as a benign lesion as cancer is not known to arise from this benign keratosis (Fig 8).

Reverse smoker's keratosis

This is serious potentially malignant lesion encountered in people who place the glowing end of the cigar or cigarette inside the mouth. The clinical appearance is often a mixture of red and white plaques. Excrescences are found within the lesion corresponding to inflamed minor salivary glands. Whereas aforementioned smoker's palate is not considered as a precancerous lesion palatal changes in reverse smokers is a high risk lesion that is associated with cancer development.

Aetiopathogenesis

Tobacco smoking (i.e., cigarette, pipe or cigar smoking) particularly when combined with heavy alcohol consumption has been identified as the primary risk factor for approximately 80% of oral malignancies. The risk of oral and pharyngeal cancers is similar for cigarette and cigar smokers, with an overall risk seven to ten times higher than for never smokers. This is not surprising as the oral cavity is exposed to the carcinogens in smoke whether the smoke is inhaled or not. When the frequency of daily tobacco use is computed there is strong dose response relationship between smoking rates and risk of mouth cancer. Addition of ST to the areca quid raises the relative risk of the product by nearly 15 times.

Case-control studies from Europe have reported adjusted odds ratios (ORs) of 11.1 for oral cavity and 12.9 for pharyngeal cancer. In particular, smoking frequency and duration, and age at start have significant associations. After giving up tobacco for a decade or so the risk of oral cancer of a past smoker drops significantly to levels almost comparable to never smokers.

Smoking patients show reduction of inflammatory clinical signs that might be associated with local vasoconstriction from nicotine, influence on vasculature and cellular metabolism. This may suppress symptoms of gingival inflammation. Pathogenesis of periodontitis in smokers could be linked to defects in neutrophil function, impaired serum antibody responses to periodontal pathogens and potentially diminished gingival fibroblast function suggesting altered host response and susceptibility. It is claimed that among smokers, more patients remain culture positive for periodontal pathogens after therapy. This may contribute to the often observed unfavourable treatment results among non-compliant smokers.

Diagnosis

Detection of tobacco consumption is mostly based on taking a social history. This should include questions on type of tobacco habit, daily frequency and duration of use. Age of commencement is also an important risk factor for many disorders and should be recorded. Current smokers could be regular or occasional smokers, regular being daily smokers. Some have the habit of binge smoking when consuming alcohol only but are unlikely to be addicted to tobacco.

Tobacco handling can usually be seen on heavily smoking patients' fingers and the tobacco stains on the oral mucosa and teeth. Dorsal tongue is often stained in many smokers. A bad breath can also highlight a smoker.

Validation of smoking can be done using the carbon monoxide breath test (piCO, Bedfont) or by measuring salivary, urine or serum cotinine which is a metabolite of nicotine. Cut off concentration of salivary cotinine is taken as 14 ng/ml to detect a regular smoker.

Level of dependence to tobacco can be assessed using the Fagerström test.

Treatment and interventions

Tobacco dependence shows many features of a chronic disease. Regular smokers are addicted to the habit as tobacco use results in true drug dependence. A minority is able to quit in one attempt but the majority may need some assistance to cease tobacco use. Numerous effective treatments are now available, and the dentists, oral physicians and their team members should become actively involved in efforts to reduce smoking. Smoking cessation advice delivered by dentists have shown to be effective. Brief advice given by a clinician lasting about 3 minutes can yield a cessation rate up to 5%. With additional support such as recommended use of nicotine replacement therapy the quit rates achieved could be doubled. In treating a smoker (willing to quit) the 5A's, designed as a brief counseling intervention, is helpful:

1. **A**sk about tobacco use - every patient/every visit
2. **A**ssess willingness to make a quit attempt
3. **A**dvice (those willing) to quit tobacco use. Those unwilling will need motivation to return to the topic at a later time

4. **A**ssist in quit attempt - set a quit date, emphasize total abstinence, prompt support seeking, provide supplementary material and recommend pharmacotherapy (see below)
5. **A**rrange follow up and refer to a specialist clinic if the quit attempt has failed

Pharmacotherapy

As with other chronic diseases, the most effective treatment of smoking requires multiple approaches in addition to clinician's advice. Pharmacotherapy is proven to be effective, and several products are available; nicotine patches, nicotine gum, nicotine lozenge, nicotine inhaler and nicotine nasal spray.

Non-nicotine medication approved for smoking cessation is bupropion (Zyban) therapy starting one week before the quit date and continued up to 12 weeks after quitting. There are several medical contra-indications particularly those with a predisposition to seizures and/or a history of epilepsy. Pregnant and breast-feeding mothers should not be prescribed this drug. Bupropion therapy increases the chances of quitting considerably up to 30% giving up smoking.

Prevention

Prevention of tobacco use is a key element in public health. As tobacco use and experimentation starts in early life preventive approaches should be appropriately targeted to young people. Paedodontists, orthodontists, school dentists and family practitioners can take steps to initiate advice to young children never to start smoking. Banning tobacco smoking in public places, legislation on tobacco advertising and taxation are known to effect tobacco sales. Primary prevention, the helping of people not to use tobacco in the first place and assisting current smokers to quit, is an effective way to reduce morbidity and mortality from oral cancer.

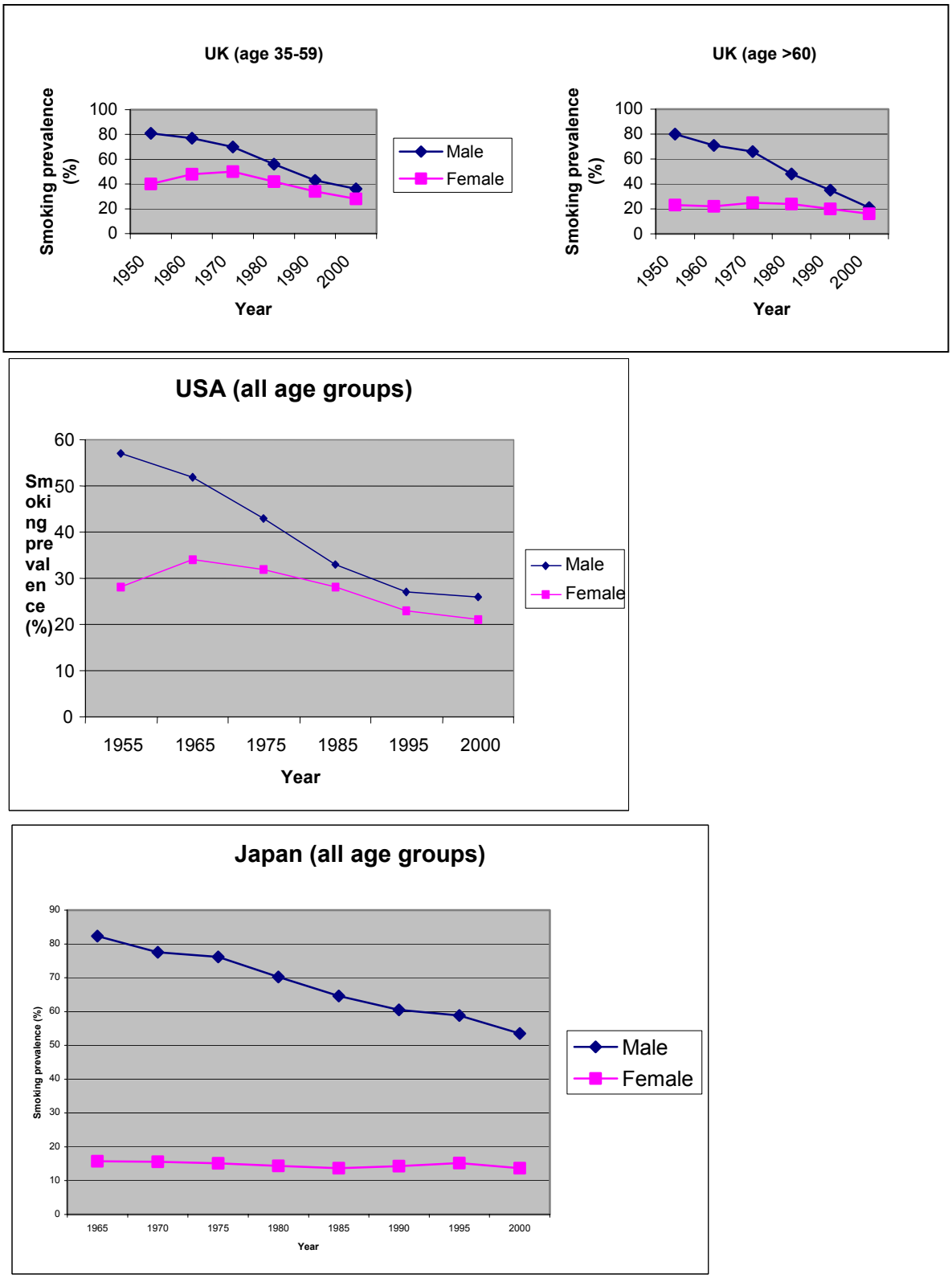

Figure 1. Trends of smoking in USA, UK and Japan by sex.

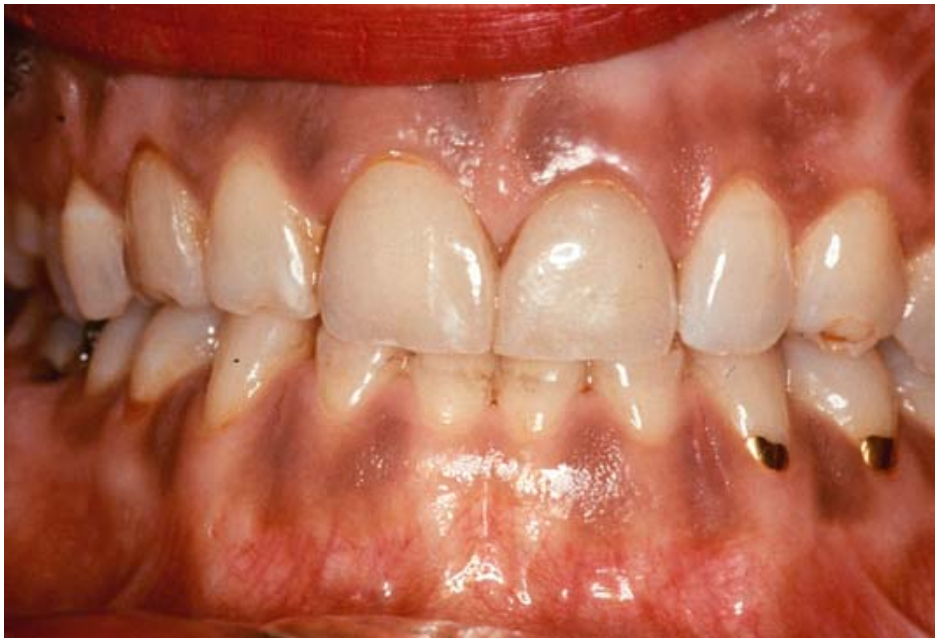

Figure 2. Diffuse melanin pigmentation on the gingiva in a Danish heavy smoker.

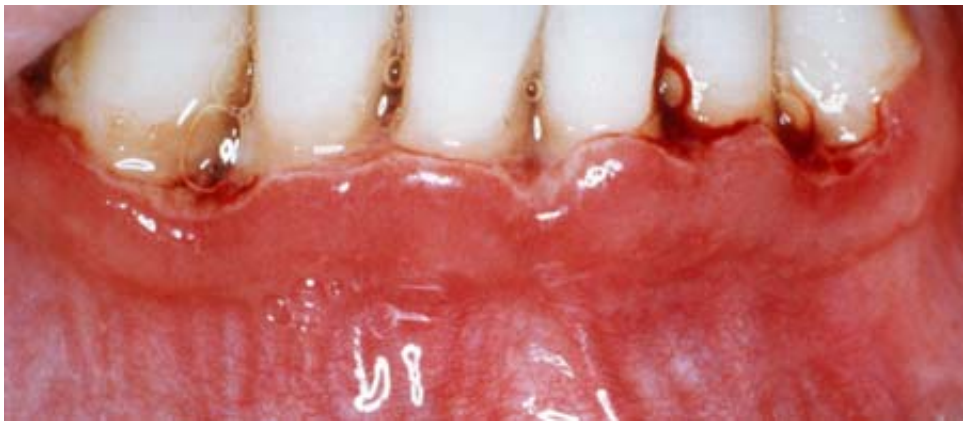

Figure 3. Acute necrotising ulcerative gingivitis showing destruction of the interdental papillae, pseudomembrane, and spontaneous bleeding.

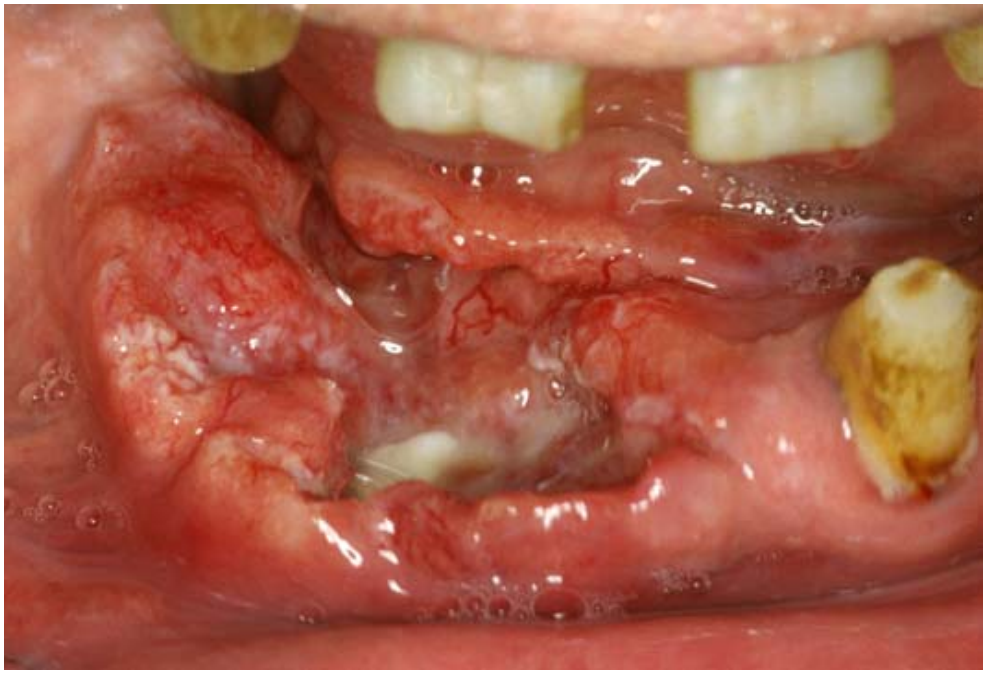

Figure 4. Cancer (squamous cell carcinoma) of the floor of the mouth/alveolar process in a heavy smoker.

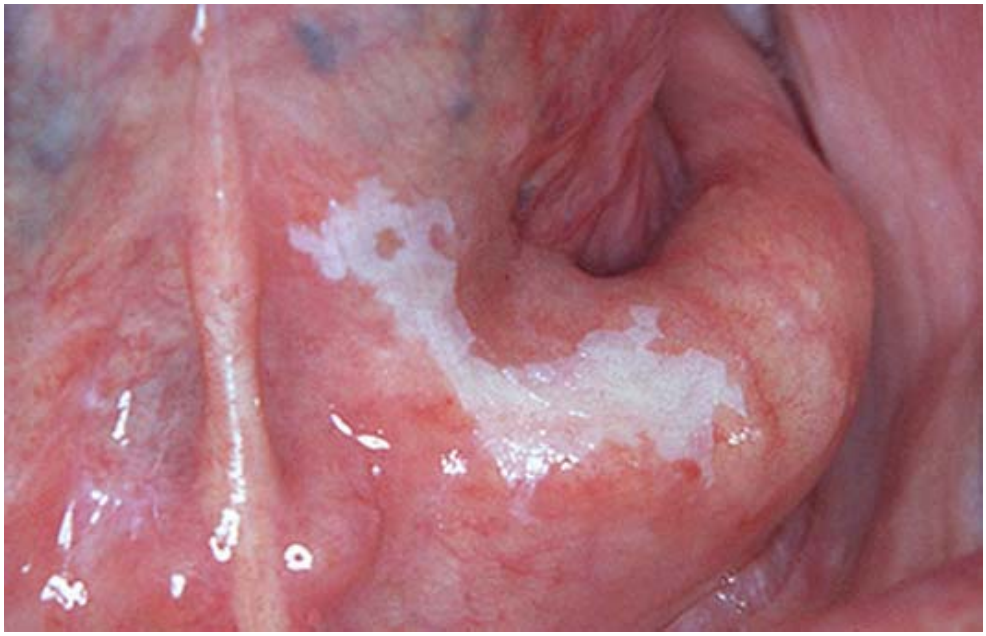

Figure 5. Homogeneous leukoplakia in the floor of the mouth.

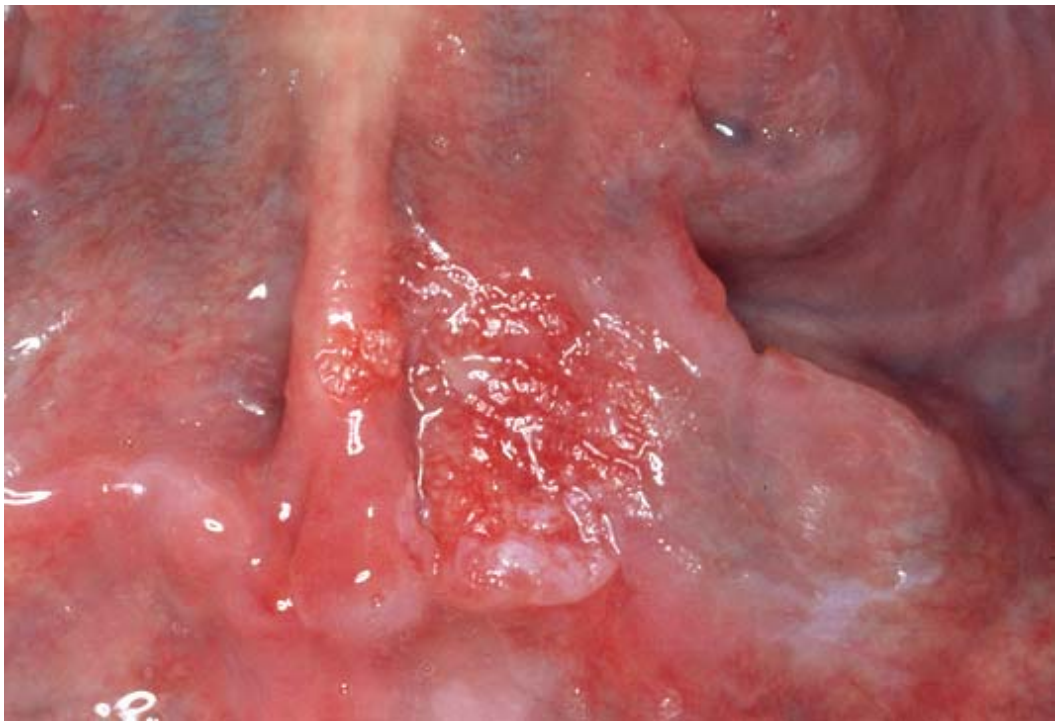

Figure 6. Non homogeneous leukoplakia in the floor of the mouth presenting with whitish, reddish, and nodular features.

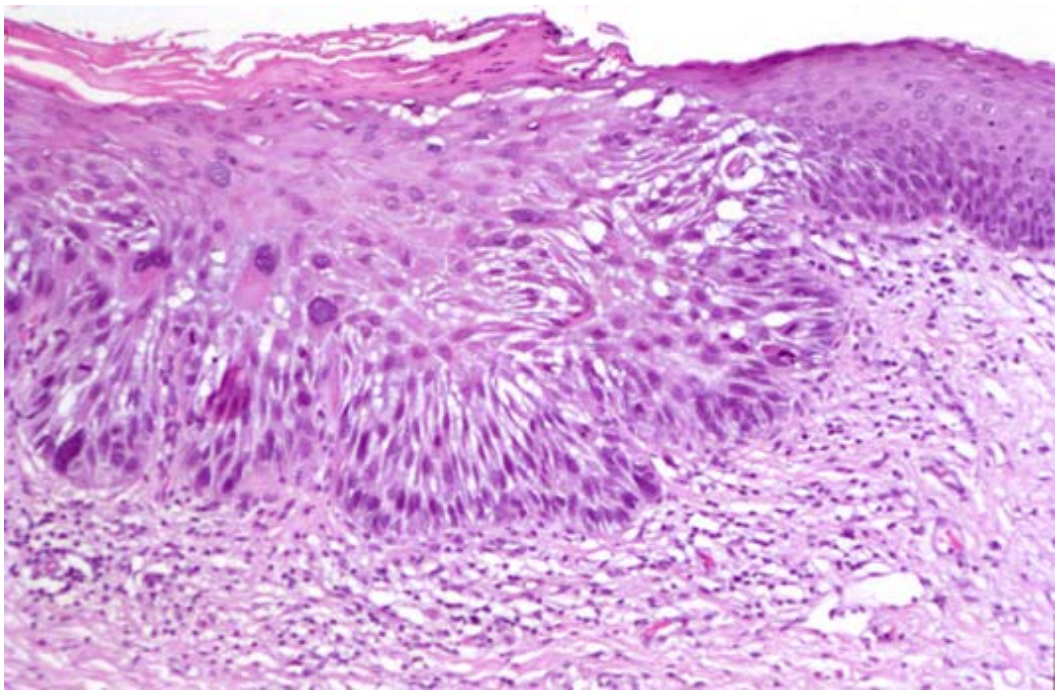

Figure 7. Biopsy of non homogeneous leukoplakia of the floor of the mouth showing severe epithelial dysplasia. Normal epithelium in right part.

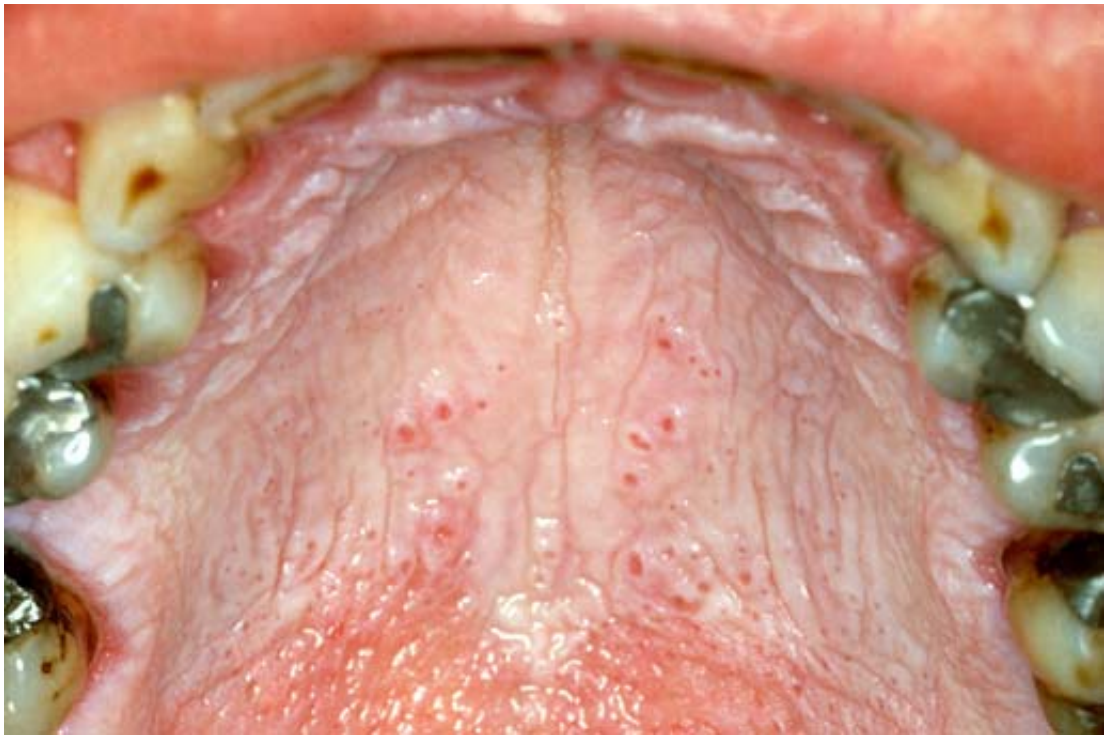

Figure 8. Smokers palate in a pipe smoker.

Further reading

1 World Health Organization. Addressing the Worldwide Tobacco Epidemic through Effective Evidence-Based Treatment. Expert Meeting March1999, Rochester, Minnesota, USA. Tobacco Free Initiative, WHO 2000.

2 Tomar SL, Asma S. Smoking-attributable periodontitis in the United States; findings from NHANES III. J Periodontol 2000; 71: 743-751.

3 EU Working Group on Tobacco and Oral Health. Meeting Report. Oral Dis 1998; 4: 464-467.

4 Warnakulasuriya S. Effectiveness of tobacco councelling in the dental office. J Dent Education 2002; 66: 1079-1087.

5 Schepman KP, Bezemer PD, van der Meij EH, Smeele LE, van der Waal I. Tobacco usage in relation to the anatomical site of oral leukoplakia. Oral Diseases 2001; 7: 25-27.

6 Smith SE, Warnakulasuriya KAAS, Feyeraband C, Belcher M, Cooper DJ, Johnson NW. A smoking cessation programme conducted through dental practices in the UK. Br Dent J 1998; 185: 299-303.

Links

1. Tobacco or health: a global status report
http://www.cdc.gov/tobacco/who/

2. Tobacco Cessation Guideline
http://www.surgeongeneral.gov/tobacco/

TOOTH EROSION

Fig.1

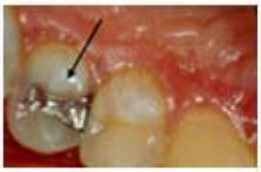

Fig.2

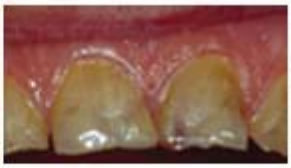

Fig.3

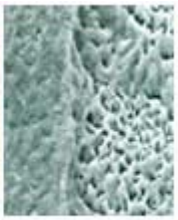

Fig.4

Fig.5

Definition

Tooth erosion is a form of tooth wear caused by the action of acid on tooth substance. This acid could be dietary, gastric or environmental. It is, therefore, distinct from those types of tooth wear that are caused by friction or mechanical wear but in many cases the clinical presentation of tooth wear results from a combination of acidic and frictional causes.

Epidemiology

Few epidemiological studies of the prevalence and severity of tooth erosion have yet been performed on a national basis. Studies have focused on small groups of patients, often pre-selected, for example because of symptoms. Thus erosion was seen largely in patients with symptoms of gastric reflux (Gastro-oesophageal reflux disease or GORD) and later was recognised in patients with anorexia or bulimia or in patients with unusual dietary habits. It can also be a problem in alcoholics.

In some cases erosion has been recognised as an occupational disease where workers have been exposed to acidic fumes, for example in factories making batteries. It is also an occupational disease among wine-tasters and may be seen in professional swimmers who use chlorinated swimming pools.

Over the last 10-15 years, however, there has been a steady increase in reports of erosion seen especially in young adults, adolescents and young children. Studies from Switzerland, UK, Republic of Ireland, The Netherlands and Iceland suggest that some signs of erosion can be seen in 20-40 % of subjects but severe erosion into dentine or even into the pulp is perhaps seen in 5% of subjects. The cause of this erosion, especially in children, adolescents and young adults has been largely linked to the high consumption of soft drinks, both fruit juice and carbonated drinks, by these age groups. This link has been made largely in Europe and the problem has received little attention in the literature coming from the USA.

Clinical presentation

Erosion may present on the anterior and posterior teeth and may be limited to the enamel only (Figure 1) or also affect dentine to a greater or lesser extent. Frequently, erosion is seen affecting the palatal surfaces of four maxillary incisor teeth. Erosion in the molar and premolar teeth may present as dish-like depressions on the occlusal surfaces, usually extending into dentine. If teeth have been restored prior to erosion occurring, the restorations stand proud of the surrounding enamel (Fig. 2). There may be a loss of vertical dimension and, particularly, a pattern of tooth wear involving the palatal surface of

maxillary molar teeth, buccal surfaces of mandibular molars and palatal wear of maxillary anterior teeth. This pattern is strongly suggestive of erosion caused by gastric acid. Nevertheless, other factors may play a part in the overall clinical picture. If there is a loss of occlusal enamel in the molar teeth the consequent loss of vertical dimension may produce “step-like” wear facets palatally on the maxillary anterior teeth, especially if the enamel has also been lost on these surfaces. Erosion in the maxillary anterior teeth may be so severe that it extends close to, or even into, the pulp. Rapidly progressing erosion may cause hypersensitivity of the teeth but commonly the progress is too slow for symptoms to arise. Nevertheless, patients may complain of discomfort in their teeth during eating or drinking and of increased sensitivity to cold stimulation.

Lesions of erosion are first detectable as a loss of enamel lustre and a matt appearance of the enamel. This progresses to clearly detectable loss of tooth substance in the enamel and then in the dentine as described above and shown in the figures. If the thinning of the maxillary anterior teeth is sufficiently great, fracture of the unsupported incisal edges may occur (Fig. 3). Erosion usually progresses quickly in dentine when other types of tooth wear become superimposed on the erosion.

Aetiopathogenesis

In recent years the high consumption of soft drinks has been the aetiological agent that has been most implicated in the upsurge of tooth erosion that has been reported particularly from Europe. Although a low salivary buffer capacity may exacerbate the effects of these acidic drinks on teeth, there is conflicting evidence in the literature concerning the contribution of a low buffer capacity to the severity or progression of erosion. It would seem logical to assume that a low buffer capacity would at least extend the time during which tooth enamel was eroded after contact with an acidic drink. Swishing a drink around in the mouth appears to increase the severity of erosion while drinking through a straw reduces the severity of erosion. Although much attention has been placed in recent years on the role of extrinsic acids, mostly from foods but also from medicines and the workplace in the causation of erosion, intrinsic acid in the form of refluxed gastric acid is still a major aetiological factor in tooth erosion. Scanning electronmicrographic appearances of eroded enamel and dentine are shown in Fig. 4 and Fig.5 respectively.

Diagnosis

Tooth erosion is one of the various manifestations of non-carious tooth destruction that have been termed *tooth wear.* Many patients present with tooth wear that is the result of several aetiological factors that do not fall conveniently into one or other of the categories, attrition, abrasion or erosion. Clinical examination is the most usual way for tooth erosion to be detected. Tooth erosion may be present in patients with gastro-oesophageal reflux disease, bulimia and anorexia. Patients undergoing cytostatic drug treatment for malignancies may suffer from frequent vomiting which rapidly may cause erosion. It is clearly important for doctors and nurses treating patients with these conditions to be aware of the possibility that the patient could also have significant tooth erosion.

The location of tooth erosion and its severity should be recorded. Several indices are available for this, ranging from the relatively simple index of Eccles and Jenkins, that was designed for recording the severity of erosion, through the more detailed modification of the same index proposed by Lussi and

the detailed Tooth Wear Index of Smith and Knight. In epidemiological studies, the degree of inter- and intra- examiner variability in detecting and scoring tooth wear may be as great a problem as determining the aetiology. Careful calibration of examiners is helpful. For an individual practitioner, study casts are a useful record of the status at any particular time and can be used to monitor progression of erosion. Computer-aided image analysis of impressions or study models is being developed and may become useful clinical tools for recording progression of erosion.
Good history taking is essential to determine the consumption of acidic drinks, and other dietary factors that may contribute to the observed erosion. Medication, particularly frequent use of asthma inhalers containing steroid or effervescent medications, should be checked as they may contribute to tooth erosion. The possibility of gastro-oesophageal reflux should be considered, not only bulimia and anorexia that patients are understandably reluctant to admit to, but also other possible causes of reflux including hiatus hernia. It may be necessary for the dentist to refer the patient to a gastroenterologist for investigations including gastroscopy and 24-h monitoring of oesophageal pH that is the “gold standard” for diagnosis of gastro-oesophageal reflux disease. Prompt diagnosis of reflux will in most cases lead to medication or possibly surgery to reduce reflux that will, in turn, remove the erosive challenge to the teeth.

Treatment

Restorative treatment of teeth affected by tooth erosion is often complex and very expensive, especially if occlusal erosion has caused a significant reduction in vertical dimension. As there are few long-term studies on how tooth erosion and related tooth wear progresses in young people, recommendations on restorative measures are difficult to make. Various non- or minimally-invasive procedures have been tried in order to prevent further tooth wear but clearly extensive crown and bridge work is sometimes required. As the durability of crown and bridgework is limited and patients with erosion are often young, conservative approaches that may also offer a degree of protection or prevention against further wear are therefore urgently needed. Restorative techniques should preferably involve no further destruction of remaining tooth substance. Dentine-bonding agents have been shown to be effective in reducing sensitivity and offering protection against further dissolution of erosive lesions. These should be applied and the patient monitored before any final decision is taken on restorative measures.

Prognosis and complication

Pain or discomfort in teeth that have lost their protective enamel covering is the most common complication of erosion. Once hard tissue has been lost because of tooth erosion it will not be regained. Total destruction of the dental hard tissues is the worst scenario though seldom encountered today. Nevertheless, recognition of the problem and prompt prevention may lead to a limitation of the damage that would otherwise occur. This applies to erosion caused by intrinsic as well as extrinsic acid. Similarly preventing the other types of tooth wear, that generally proceed more rapidly once enamel has been eroded away, will improve the prognosis. It could be considered a complication of erosion that the teeth often require crowns to restore function and aesthetics. A major

complication of tooth erosion is the loss of vertical dimension caused by molar erosion. Restoring the dentition then requires the costly and technically more demanding restoration of the vertical height.

Prevention

With the high prevalence of tooth erosion recorded in some surveys, tooth erosion has now achieved the status of a community-wide dental problem in several countries. Nevertheless, true prevention is difficult to achieve. Much that can be done is aimed at limiting further erosion in individuals already found to be affected by this condition. Population-based strategies of prevention, such as widespread modification of the composition of soft drinks and educational campaigns to increase awareness of the causes of tooth wear may be possible. The groups most at risk of developing erosion are, however, teenagers and young adults, and these are rather resistant to the messages of health educators, at least when the message relates to reducing the consumption of erosive drinks that are so much a part of their lifestyle. More can possibly be done with an at-risk strategy aimed at specific individuals with early signs of erosion or with known risk factors for erosion, such as those taking erosive medicines and patients with bulimia. For such a strategy to work collaboration between the dentist and other health-care professionals is important. Topical fluoride, the mainstay of caries prevention, appears to protect against abrasion following acid challenge but has no direct effect in preventing erosion.

Drink modification has been developing in recent years with varying success. Calcium lactate has been shown to reduce the erosive potential of to Coca Cola® but this research does not appear to have been taken up by the manufacturer. The addition of calcium to low pH fruit drinks has been shown in *in-situ* and *in-vitro* studies to be less erosive than the same drinks without added calcium. Drink modification has considerable potential in combating erosion but clinical trials are needed.

Diet modification is a difficult area in which to achieve successful disease prevention. Nevertheless the strong links between dietary factors and tooth erosion make it sensible for the dental team to at least try to get patients with tooth wear to modify their diet. Consuming cheese or milk products after drinking an erosive beverage may promote re-hardening of the enamel. This is probably also a useful method of neutralising acid in the mouth after a bout of reflux or vomiting but patient compliance is perhaps questionable. Chewing-gum containing carbamide (urea) has been shown to raise salivary pH rapidly. This may, therefore, reduce the erosive effect of acid in the mouth.

The pattern of drinking erosive beverages is thought to contribute to tooth erosion especially when cola-type drinks are swished around the mouth before swallowing. Drinking through a straw has been shown to reduce the potential for tooth erosion from acidic drinks, especially on the palatal surfaces of the maxillary incisors that are most commonly affected in patients with erosion.

Dentists should advise their patients not to brush shortly after consuming carbonated drinks as this may increase loss of enamel. Similarly, mouth rinses with a low pH should not be recommended for prolonged use nor as pre-brushing rinses. Remineralizing toothpaste has been shown to increase the hardness of acid-treated teeth significantly more than conventional fluoride toothpastes in in-vitro studies.

Saliva and pellicle are important factors in protection of tooth substance against acid attack. Studies have shown that erosion is usually found in areas of the dental arches that are lacking in pellicle.

Increasing salivary flow will lead to greater accumulation of pellicle as well as increasing the buffering action of saliva and, consequently, will promote remineralization. Sugar-free chewing gum, fluoride-containing or carbamide-containing gum should be advised particularly for adolescents who may be least willing to limit their consumption of acidic beverages. A number of preparations intended to promote salivation are available for patients including those with dry mouth symptoms who may not be willing to chew gum. Profylin™ (Prophylactor AB, Sweden) and Xerodent™ (Dumex-Alpharma, Denmark) lozenges are examples of such topical preparations and Xerodent™ has the added advantage of containing fluoride.

Reflux disease and vomiting are important causes of tooth erosion. Recognition of the erosion and presumptive diagnosis by the dentist should lead to appropriate referral for further investigation. Medication to reduce gastric reflux and acid production includes drugs such as over-the-counter antacids or prescription drugs such as omeprazole (Losec®), esomeprazole (NexiumÆÊ) and ranitide (Asyran®). Antacids may help and they may be kept in the mouth for a while before swallowing for a local buffering effect. Should hiatus hernia be diagnosed then surgical intervention may be necessary.

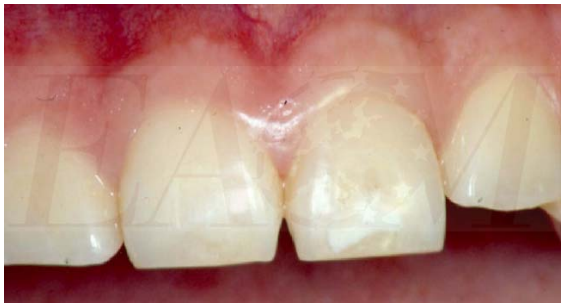

Figure 1 Characteristic smooth-appearing enamel surface of incisors, where the developmental ridges have disappeared because of erosion caused by excessive beverage use

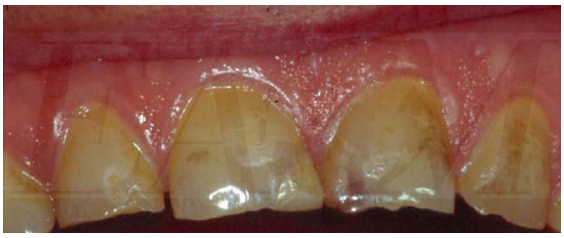

Figure 3 2nd to 3rd grade erosion of teeth of a patient with long-term bulimia. Note the irregular appearance of the incisal edges.

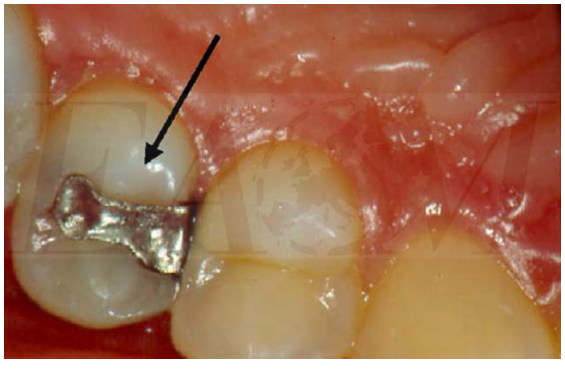

Figure 2 The arrow points at the margins of amalgam fillings, which appear elevated due to surrounding enamel dissolution caused by erosion.

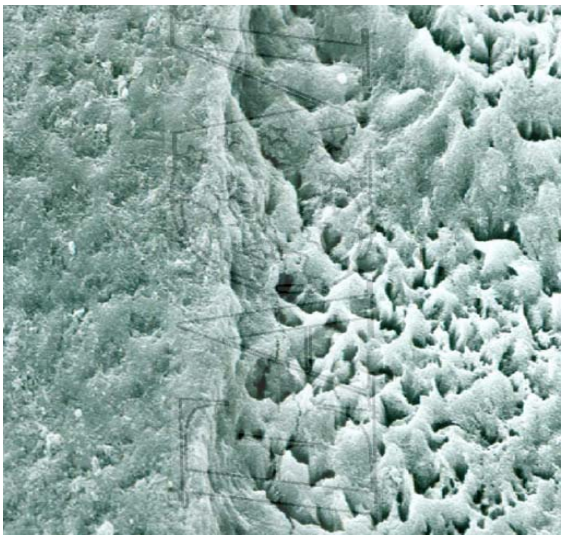

Figure 4 Scanning electron micrograph of eroded enamel (on the right) showing characteristic honeycomb structure of dissolved enamel prisms.

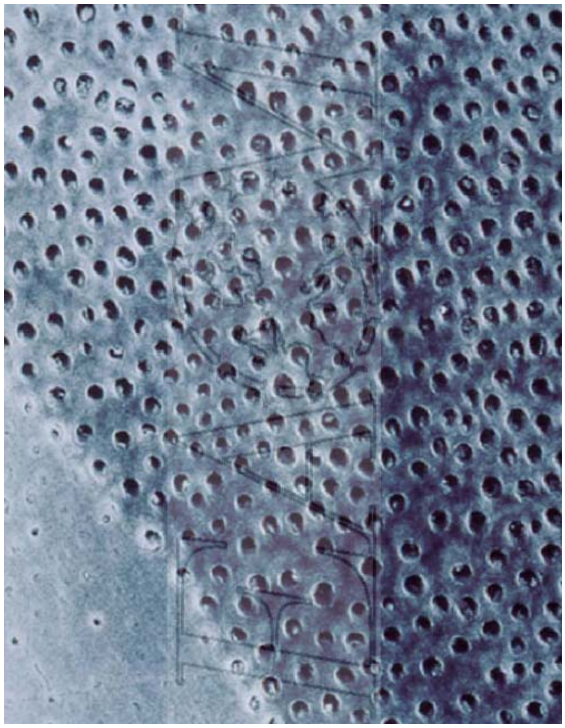

Figure 5 Scanning electron micrograph of eroded dentin (on the right) showing open dentin tubules caused by dissolution of the hard tissue

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WHITE SPONGE NEVUS

Fig.1 Fig.2 Fig.3 Fig.4 Fig.5

Definition

White sponge nevus (WSN) is a rare autosomal dominant disorder which was first described by Hyde in 1909, but the term was coined in 1935 by Cannon. It was also named as *familial white folded dysplasia.* The condition predominantly affects non-cornifying stratified squamous epithelia, such as the oral mucosa and, less frequently, extra oral sites, including the mucosal membrane of the nose, oesophagus, rectum and vulvovaginal mucosa; but not the skin. HPV 16 homologous DNA sequences in the biopsy specimen of oral WSN have been detected in one report.

Epidemiology

The onset of white sponge nevus usually occurs before 20 years of age and often in early childhood. It exhibits no race or sex predilection; however, because of this condition's autosomal dominant pattern of this transmission, several family members may manifest the disorder.

Clinical presentation

Clinically, white sponge nevus of the oral cavity is characterized by the presence of asymptomatic, bilateral, soft, white and "spongy" plaques (Figures 1-5). The surface of the plaque is thick, folded and may peel away from the underlying tissue. Lesions are asymptomatic and rough to palpation. The condition may involve the entire oral mucosa as to leave little normal mucosa visible, or may be distributed unilaterally as discrete white patches. The buccal mucosa is the most commonly affected site, followed by the soft palate, ventral tongue, labial mucosa, the alveolar ridges and the floor of the mouth. Gingival margin and dorsal aspect of tongue are usually spared. The disease is characterized by a wide variability and high penetrance, but with a benign clinical course. The size of lesions varies from patient to patient and time to time.

Aetiopathogenesis

White sponge nevus (WSN) is an inherited disorder exhibiting autosomal-dominant transmission with no sex predilection mutations. The mutations affecting keratin protein interfere with intermediate filament assembly. Thus according to a putative pathogenic mechanism, the intermediate filament can be easily damaged as a result of mild mechanical trauma, inducing cytokine flooding of underlying basal cells, and, as a consequence,

excessive basal cell proliferation leading to mucosal hyperkeratosis. Histopathological features, including epithelial thickening, parakeratosis, extensive vacuolization of the suprabasal keratinocytes

and compact aggregates of keratin intermediate filaments (KIF) in the upper spinous layers, resemble those found in epidermal disorders due to keratin defects. Suprabasal cell histopathology parallels the tissue-specific expression of keratins 4 and 13 in the differentiating cell layers. Suprabasal keratinocytes of the buccal, nasal, oesophageal and anogenital epithelia specifically express K4 and K13 and, mutations in K4 and K13 genes have been associated with white sponge nevus. Hence, the lesions are restricted to mucosal epithelia.

Diagnosis

The recognition of this disorder is important in that it must be differentiated from other congenital or familial disorders of more widespread clinical significance. The clinical appearance is so distinctive that biopsy is usually unnecessary. The diagnosis is made more certain if there is a positive family history and other mucous membranes are affected. In case of any suspicion, biopsy should be performed. The differential diagnosis of white sponge nevus includes oral lesions of leukoplakia, chemical burns, trauma, syphilis, tobacco and betel nut use. White sponge nevus may also be confused with candidiasis, but fungal examination, the histology of biopsy specimens, and the response to antifungal agents will be the differentiating factors. Cheek- biting, lichen planus, lupus erythematosus should also be excluded.

Lesions of panchyonychia congenita, hereditary benign intraepithelial dyskeratosis, Darier's disease, dyskeratosis congenita may resemble lesions of white sponge nevus. Except for lichen planus and lupus erythematosus which may be limited to the oral cavity, these disorders can be distinguished clinically from white sponge nevus by their associated extra oral lesions. Thus, concurrent skin lesions exclude the diagnosis of white sponge nevus. The histopathology of these conditions also vary.

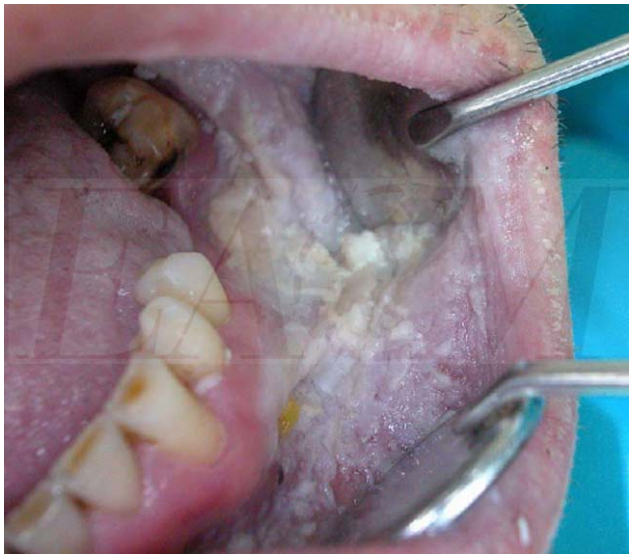
Treatment

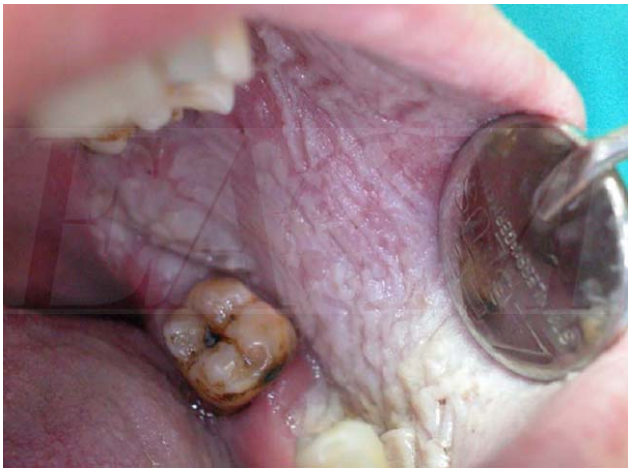
Although the patients suffer from no pain, they often complain of an altered texture of the mucosa or that the lesions are unaesthetic. Reassurance is all that is required, although numerous therapy models have been tried. None are likely to be effective unless they take into account the genetic nature of the lesions. Treatment with vitamins, antihistaminics and mouth rinses have been recommended, but none has been successful. Penicillin was reported to succeed to a little extent in the management of WSN. Treatments in the form of

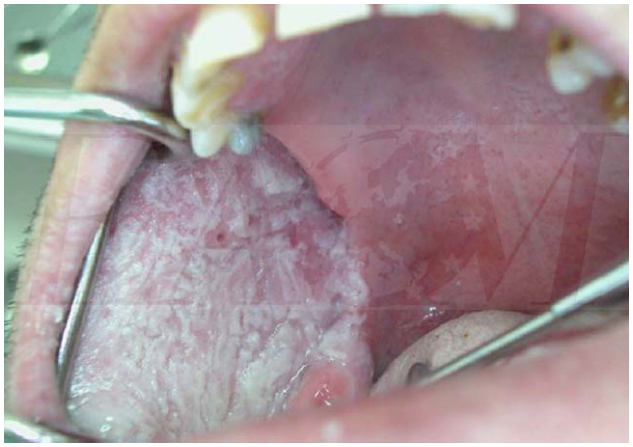
gene therapy is difficult for a group of disorders including WSN due to autosomal dominant inheritance and the mutations acting in a dominant negative-manner. To achieve this the ways of inactivating mutant gene are actively being studied.

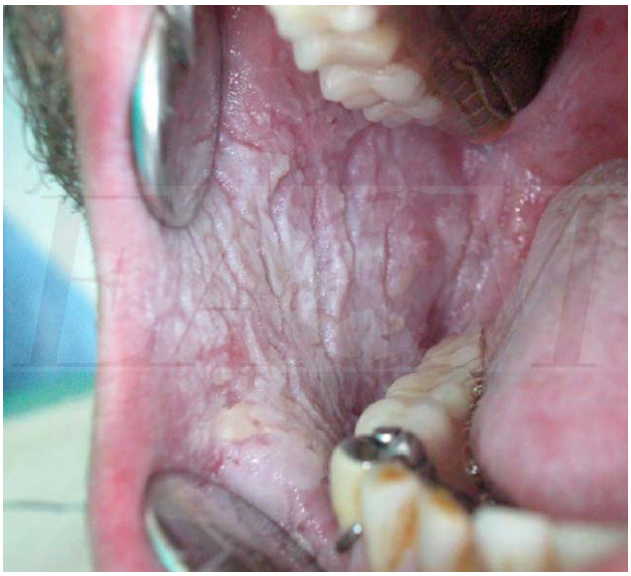
Prognosis and complications

The lesions on mucous membranes persist through life, but the condition is benign.









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