Allergic and immunologic disease of oral cavity.

DEPARTMENT OF ORAL AND MAXILLOFACIAL PATHOLOGY & ORAL MICROBIOLOGY

- ‘Allergy’ is a broad term used generally to encompass the hypersensitive state acquired by exposure to a specific material, and the altered capacity of the living organism to react upon re-exposure to it.
- There are two general types of allergic reaction-

1. Immediate reaction
2. Delayed reaction

Recurrent Aphthous Stomatitis (Aphthous ulcers, aphthae, canker sores)

- Recurrent aphthous stomatitis (RAS) is an unfortunately common disease characterized by the development of painful, recurring solitary or multiple ulcerations of the oral mucosa.

- **Etiology-** Numerous possible etiologic factors have been suggested in the interesting history of recurrent aphthous stomatitis and these have been adequately reviewed by Ship and his group,

Bacterial Infection-

- A pleomorphic, transitional L-form of an alpha-hemolytic Streptococcus, Streptococcus sanguis, as the causative agent of the disease.

- There is a T cell-mediated response to Streptococcus sanguis that produces cross-reaction between streptococcal heat shock protein and oral mucosa, leads to mucosal damage.

Genetic History.

- There is a positive family history and occurrence of RAS is associated with HLA- B51. Further, these individuals with positive family history develop the ulcers at an early stage of their life.

Precipitating Factors.

- A variety of situations have been repeatedly identified immediately preceding the outbreak of aphthous ulcers in relatively large numbers of patients and are discussed below.

Trauma

- Local trauma has been found to be the precipitating factor in nearly 75% of cases in a series reported by Graykowski and his coworkers. The traumatic incidents included self- inflicted bites, oral surgical procedures, toothbrushing, dental procedures, needle injections, and dental trauma.

Endocrine Conditions.

- It has been recognized for many years that a time relationship exists between the occurrence of the menstrual period and the development of aphthous ulcers.
- It has also been reported that women may have remission of their aphthous lesions during pregnancy but show eruptions following parturition, sometimes very rapidly.
- On rare occasions, the onset of the disease has been associated with **menarche and menopause.**

psychic factors in certain oral diseases is well recognized. In cases of aphthous ulcers, acute psychologic problems appear many times to have precipitated attacks of the disease, although this is a difficult factor to analyze.

Allergic Factors Many patients with recurrent aphthous ulcers have a history of asthma, hay fever, or food or drug al- lergies. This may be a purely fortuitous finding because of the high incidence of allergies in the general population. However, the outbreak of aphthae following the use of certain foods or drugs in the same patients has been reported so frequently that allergy must be considered a precipitating factor.

Classification. Recurrent aphthous stomatitis has been classified by many investigators into four chief varieties based upon the clinical manifestations:

- Recurrent aphthous minor, which is the most common form of the disease and the one referred to by the lay public as the ‘canker’ sore.

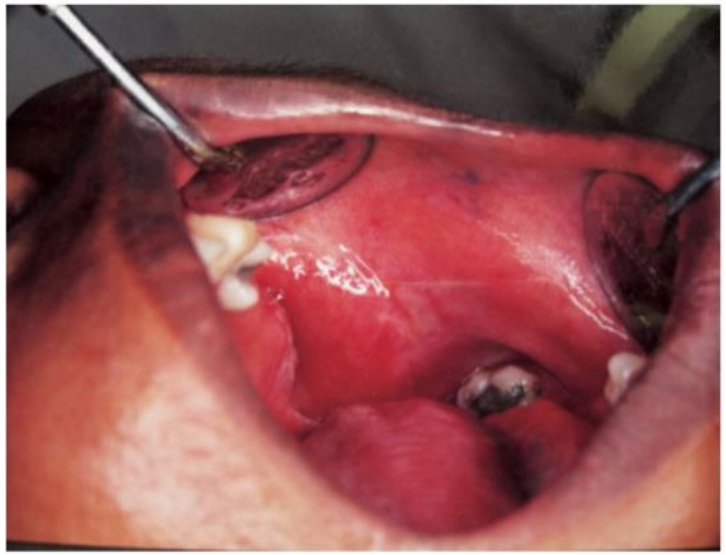
- Recurrent aphthous major, which is now believed to be simply a more severe form of recurrent aphthous minor but which was thought at one time to represent a sepa- rate disease entity known as periadenitis mucosa necrotica recurrens (Mikulicz’s scarring aphthae or Sutton’s disease).

Clinical Features.

Recurrent aphthous minor occurs somewhat more frequently in women than in men, and the majority of patients report the onset of the disease between the ages of 10 and 30 years

- The onset of the disease may occur with a variety of manifestations, which are not invariably present in all cases.
- These include the occurrence of one or more small nodules; burning sensation, erythema, generalized edema of the oral cavity, especially the tongue; paresthesia; malaise; low-grade fever; localized lymphadenopathy; and vesicle-like lesions containing mucus.

apthous ulcer minor



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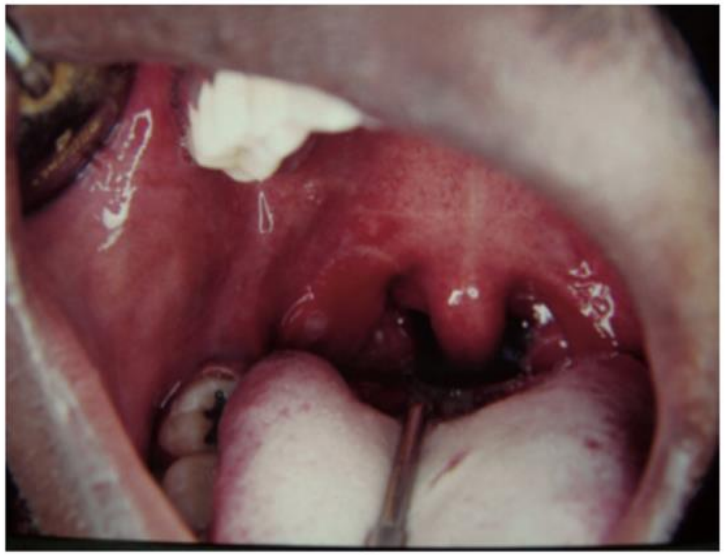

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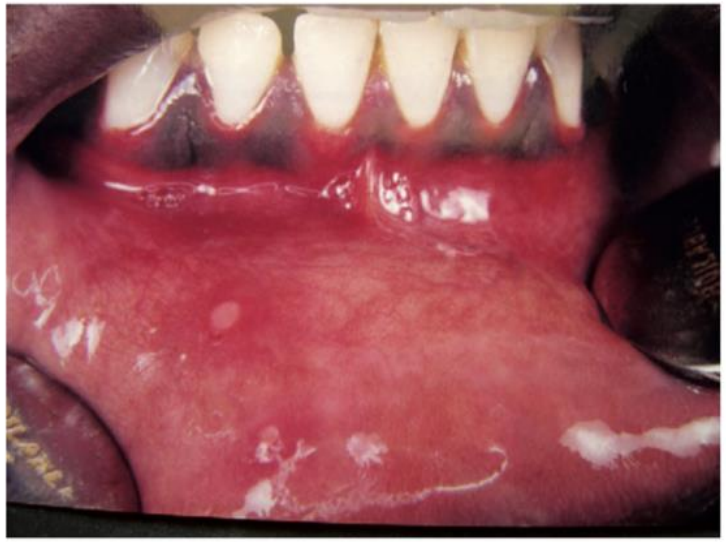
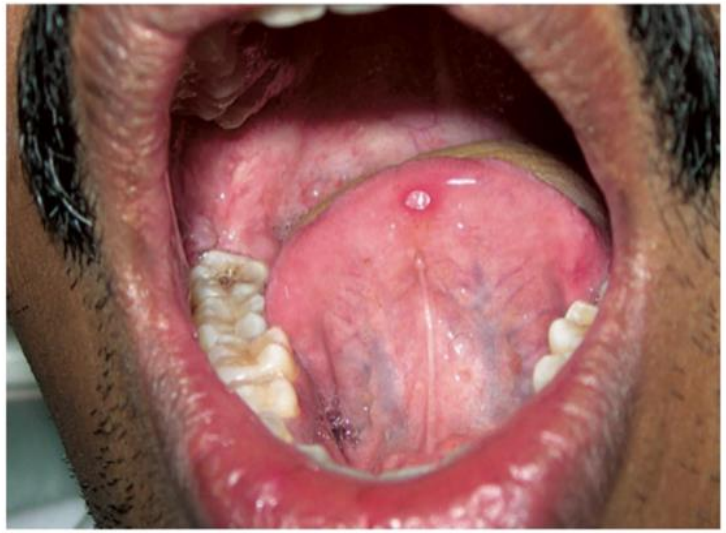


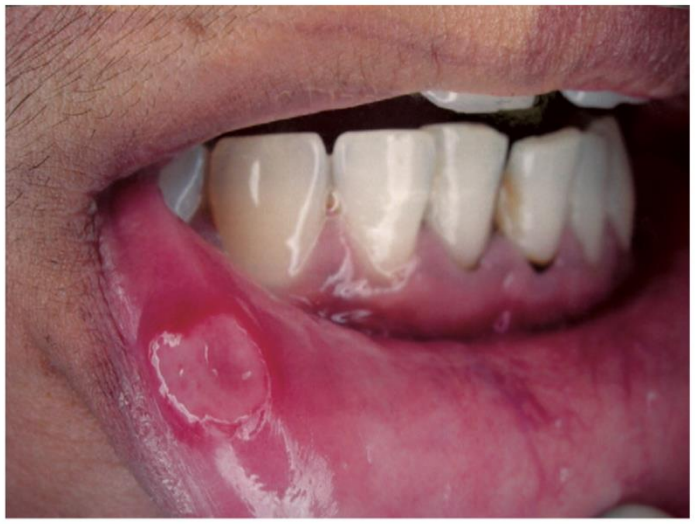


- The aphthous ulcer begins as a single or multiple superficial erosions covered by a gray membrane
- It generally has a necrotic center with clearly defined raised margins surrounded by an erythematous halo. The lesion is typically very painful so that it commonly interferes with eating and speech for several days.
- At one time it was thought that the aphthous ulcer begins with the formation of a vesicle, as does the lesion of herpes simplex infection.

- The ulcers themselves generally persist for 7 to 14 days and then heal gradually with little or no evidence of scarring.

Recurrent aphthous major is characterized by the occurrence of large painful ulcers, usually 1 to 10 in number, on the lips, cheeks, tongue, soft palate, and fauces and cause severe pain and dysphagia

Their incidence is more in patients with HIV infection.



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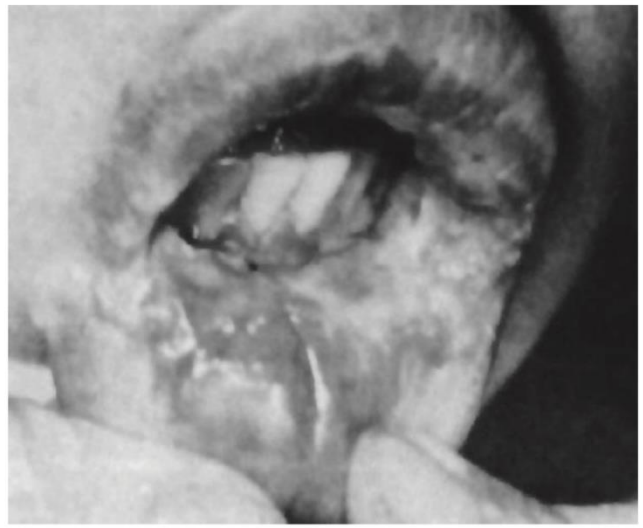


B

igure 16-2. Recurrent aphthous ulcers, major.
eep crateriform ulcer (A) and scars (B). *(B, Courtesy of Dr TH Century).*

- These ulcers occur at frequent intervals, and many patients with this disease are seldom free from the presence of at least one ulcer. Usually these lesions occur after puberty and persist up to 20 years or more.

- Unlike the typical ulcers of recurrent aphthous minor, these lesions may exceed one cm in diameter and persist for up to six weeks and leave a scar.

Recurrent herpetiform ulcers are characterized by crops of multiple small, shallow ulcers, often up to 100 in number, which may occur at any site in the oral cavity.

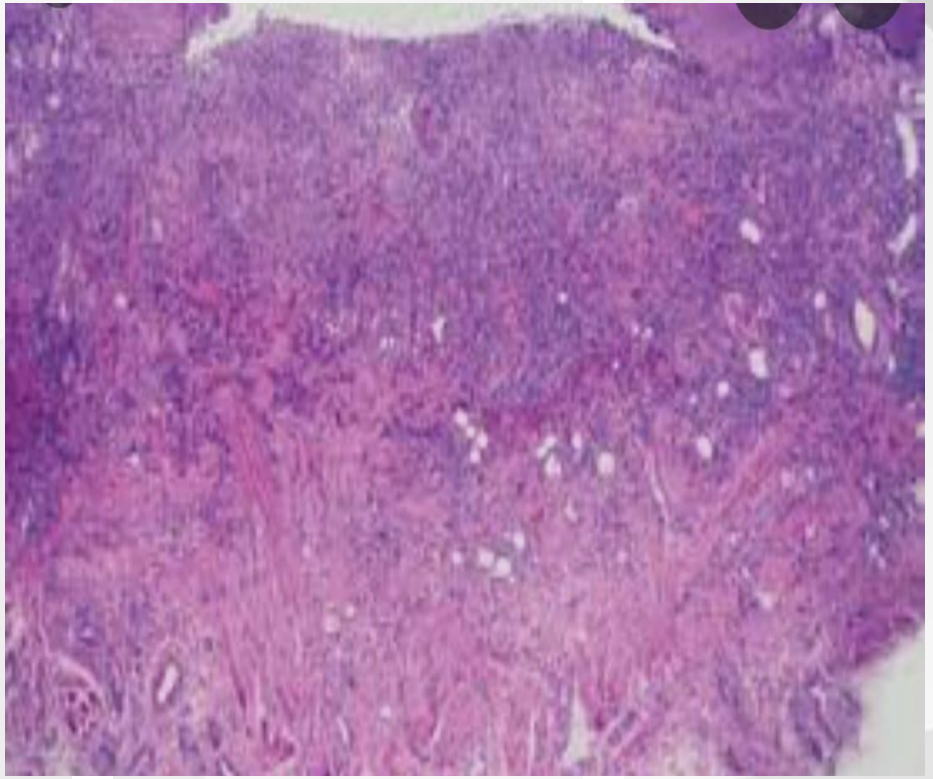
- Cooke pointed out the clinical similarities of this disease to the lesions of herpes simplex and that the corresponding histologic changes were not similar, since these lesions resemble the recurrent aphthous ulcer rather than a viral lesion.
- lesions have female predisposition with later age of onset and are not associated with herpes virus.

The characteristic clinical features of this uncommon condition were listed by Brooke and Sapp as follows:

- Numerous small lesions may be found on any intraoral mucosal surface.
- Lesions are more painful than would be suspected by their size.
- Lesions begin as small pinhead-sized erosions that gradu- ally enlarge and coalesce.
- Lesions are present almost continuously for one to three years, with relatively short remissions.

Histologic Features. The minor aphthous ulcer of the oral mucous membrane exhibits a fibrinopurulent membrane covering the ulcerated area. Occasional superficial colonies of microorganisms may be present in this membrane.

- An intense inflammatory cell infiltration is present in the connective tissue beneath the ulcer, with considerable necrosis of tissue near the surface of the lesion, neutrophils predominating immediately below the ulcer but lymphocytes prevailing adjacent to this.
- Granulation tissue may be noted near the base of the lesion. Epithelial proliferation is present at the margins of the lesion, similar to that found in any nonspecific ulcer.



Differential Diagnosis. Lesions which may be mistaken for recurrent aphthous stomatitis include herpetic stomatitis, herpangina, erythema multiforme, erosive lichen planus, pemphigus and pemphigoid.

Treatment

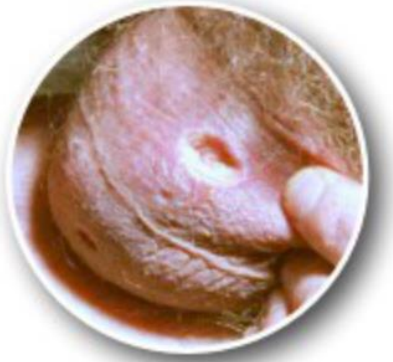
- Thereisnospecifictreatmentforrecurrentaph- thous ulcers although, over the years, many drugs have been advocated.
- An excellent summary of the many drugs and chemicals which have been used to treat recurrent aphthous stomatitis over the years has been prepared by Antoon and Miller and is shown in Table

Table 16-1: Treatment modalities for recurrent aphthous stomatitis

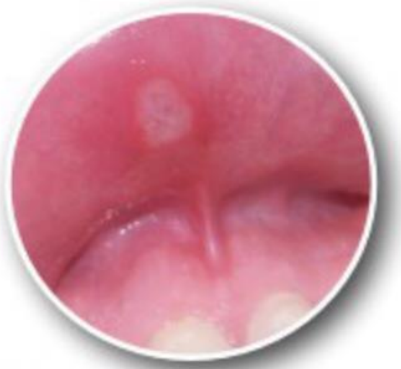
Immune enhancement
Levamisole
Vaccine
Immunosuppression, inflammatory suppression
Prednisone
Triamcinolone acetonide
Betamethasone-17-benzoate
Antihistamine
Antibiotics (Tetracycline?)
Suspension, topical
Chloramphenicol
Broad-spectrum antibiotics
Antiseptic
Silver nitrate
Coagulating agent, negatol
Gentian violet
Diet supplementation (Lactobacillus?)
Vitamin B_{12}, folic acid
Iron
Zinc sulfate
Symptomatic treatment
Xylocaine/lidocaine
Silver nitrate
Benadryl, topical
Camphor-phenol

Behçet syndrome

Relapsing uveitis

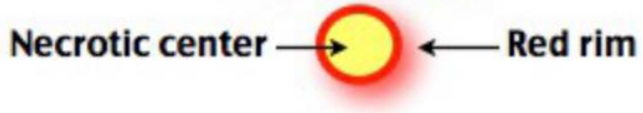


Recurring genital ulcers



Recurring oral ulcers

Painful Ulcers



Behçet's Syndrome

- Behçet's syndrome is a multisystemic, chronic disorder, characterized by oral and genital aphthous ulcers, arthritis and cutaneous lesions, ocular, gastrointestinal and neurological manifestations.

- The etiology of Behçet's disease remains obscure but various reports suggested that an infectious trigger with inflammatory mediators and immune deregulation is the causative factor in a genetically succepted host.

- Streptococcus sanguis and S. oralis can be found in the oral microbiota of Behçet's syndrome patients and other agents include the hepatitis virus, parvovirus B19; some bacteria, including mycobacteria, Borrelia burgdorferi, Escherichia coli, Saccharomyces cerevisiae fungus may be elevated with the occurrence of this disease.

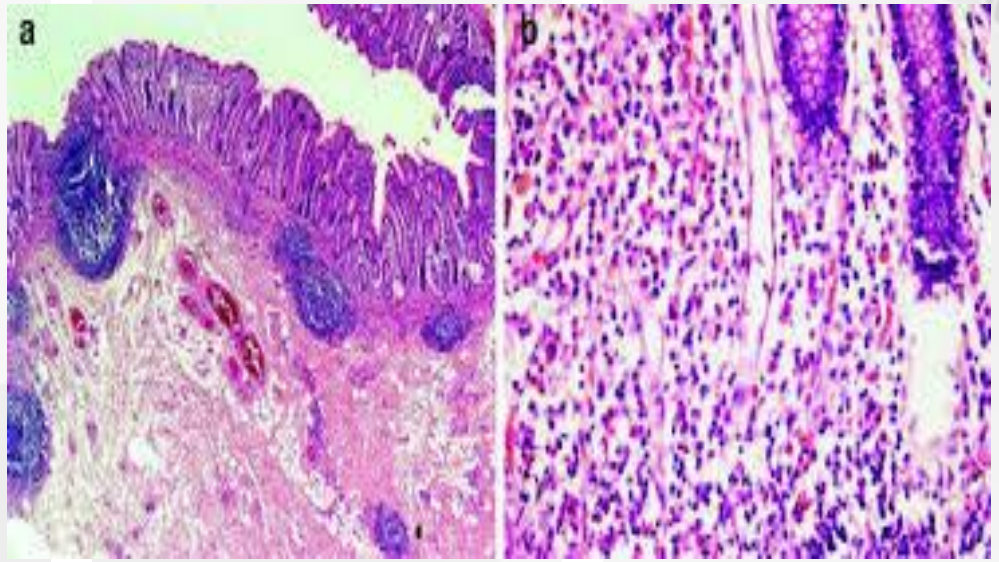
Clinical Features

- Behçet's syndrome is characterized by exacerbations and remissions. The duration of attacks ranges between few days to few weeks.

- This syndrome is more common in young adults between the ages of 25 and 40 and is 5 to 10 times more common in **males**
- It is characterized chiefly by **oral and genital ulcerations, ocular lesions, and skin lesions.**
- The first manifestation of the disease is usually the appearance of oral and/or genital lesions.
- The oral lesions are painful and very similar clinically and histologically to that of recurrent aphthous ulcers. They occur in crops at any intraoral site and consist of ulcers **ranging in size**

Histologic Features.

- The intraoral ulcers are entirely nonspecific, and according to Lehner, are remarkably similar to recurrent aphthous ulcers. Endothelial proliferation is reported in the lesions of Behçet's disease but not in the recurrent aphthous ulcer. Vasculitis also appears to be an essential lesion in Behçet's disease.



Treatment and Prognosis.

- There is no specific treatment for the disease other than symptomatic or supportive measures. While Behçet's disease may undergo spontaneous remission after a variable period of months to years, it may progress to serious complications and even result in death.

Reiter's Syndrome

- Reiter's syndrome is associated with urethritis, balanitis, conjunctivitis, and mucocutaneous lesions.

- It is a disease of unknown etiology, although there is evidence of an infectious origin.
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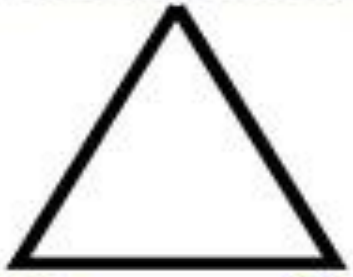
- **HLA-B27 is considered to be a disease susceptibility factor in Reiter's syndrome.**

- This disease is also seen frequently in HIV positive patients.

Reiter's syndrome

Triad of :

Asymmetrical arthritis

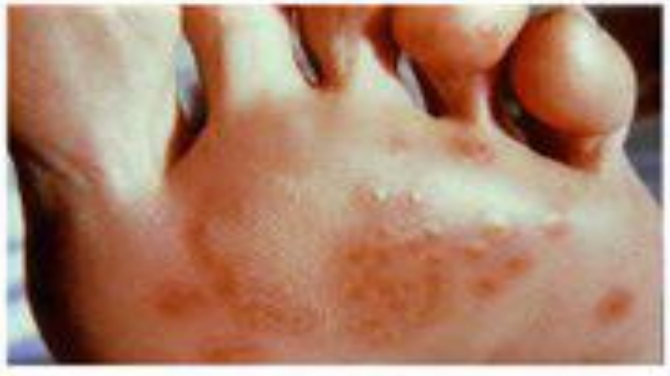


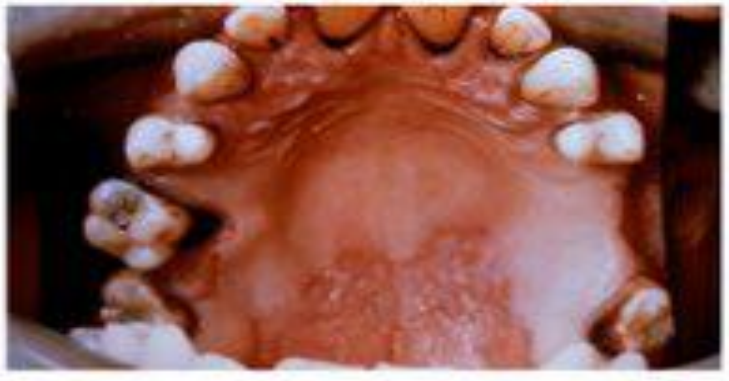
Urethritis/cervicitis or Diarrhoea

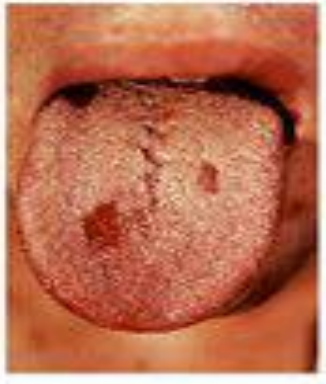
Conjunctivitis

May be associated with :

- Mucocutaneous disease
- (balanitis, ulcers, keratoderma)







Clinical Features.

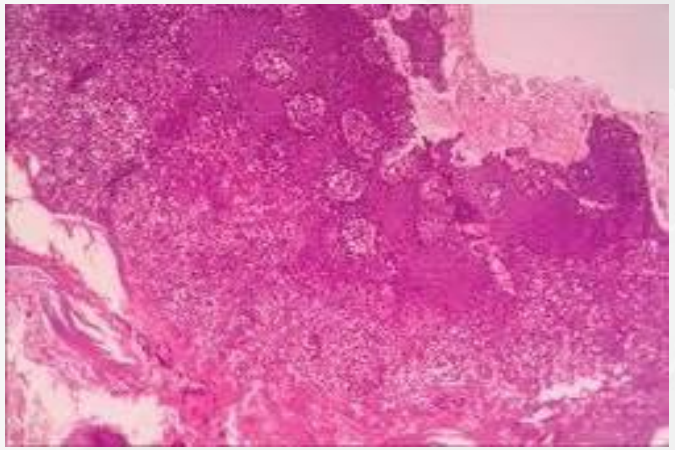
- Reiter's syndrome is more prevalent in young adult men, usually between 20 and 30 years of age.
- The male to female ratio is 9:1.
- There is a typical tetrad of manifes- tations: nongonococcal urethritis, arthritis, conjunctivitis, and mucocutaneous lesions.
- Urethritis may be the first sign. The urethral discharge is usually associated with itching and burning sensation.
- The arthritis is often bilaterally symmetrical and usually polyarticular. Conjunctivitis is often so mild as to be overlooked.
- The skin lesions are similar to those seen in keratoderma blennorrhagica and consist of red or yellow keratotic macules or papules which eventually desquamate.

Oral Manifestations.

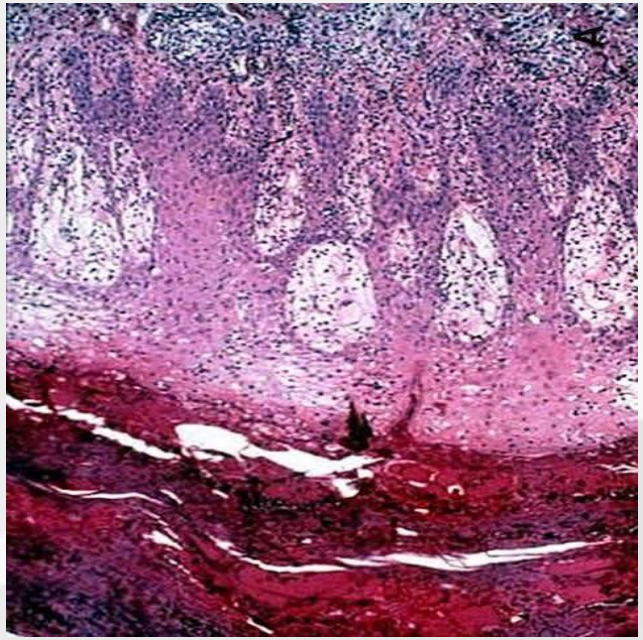
- painless, red, slightly elevated areas, sometimes granular or even vesicular, with a white circinate border on the buccal mucosa, lips, and gingiva.
- They may be mistaken for recurrent aphthous ulcers.
- The palatal lesions appear as small, bright red purpuric spots which darken and coalesce, while the lesions on the tongue closely resemble ‘geographic’ tongue.
- Clinically, similar lesions occur on the glans penis, producing a circinate balanitis.

Histologic Features

- They consist of parakeratosis, acanthosis and polymor- phonuclear leukocyte infiltration of epithelium, sometimes with microabscess formation similar to psoriasis.



- The connec- tive tissue shows a lymphocyte and plasma cell infiltrate.



Laboratory Findings

- The patients usually have a mild leukocytosis, an elevated sedimentation rate, and pyuria.

Treatment and Prognosis

- The disease may undergo spontaneous remission but has been treated by antibiotics and corticosteroids.

Sarcoidosis

(Boeck's sarcoid, Besnier-Boeck-Schaumann disease)

- Sarcoidosis is described as a multisystem granulomatous disease of unknown origin characterized by the formation of uniform, discrete, compact, non-caseating epithelioid granulomas.
- It is more common in blacks than in whites.
- lesions of sarcoid are most common in the lungs, skin, lymph nodes, salivary glands, spleen, and bones, but may be found to involve practically any site, including the mouth.

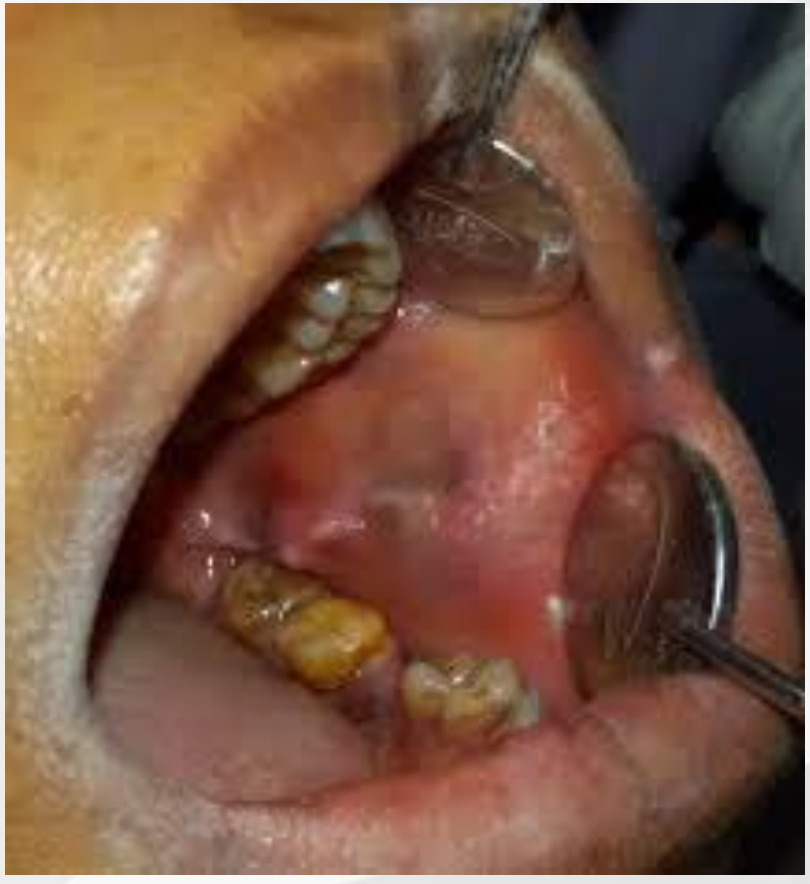
The disease is characterized by a depression of delayed-type hypersensitivity suggesting an impaired cell-mediated immunity, and raised or abnormal serum immunoglobulins suggesting lymphoproliferation.

Clinical Features-

- It is most commonly seen in young and middle-aged adults, it may occur later in life and is considerably more prevalent in blacks.
- Mild malaise and cough may be the chief features, although involvement of a specific organ may occur and be evidenced by dysfunction of that organ.
- Cutaneous lesions, which are present in approximately 25–35% of all patients with sarcoidosis, may be the only distinct manifestation of the disease.
- These appear as multiple, raised red patches that occur in groups, grow slowly, and do not tend to ulcerate or crust. Erythema nodosum occurs in about 15% of the patients.
- Involvement of lymph nodes or salivary glands is manifested only by nodular enlargement, while hepatomegaly and splenomegaly may occur, owing to the presence of the disease in the liver and spleen.

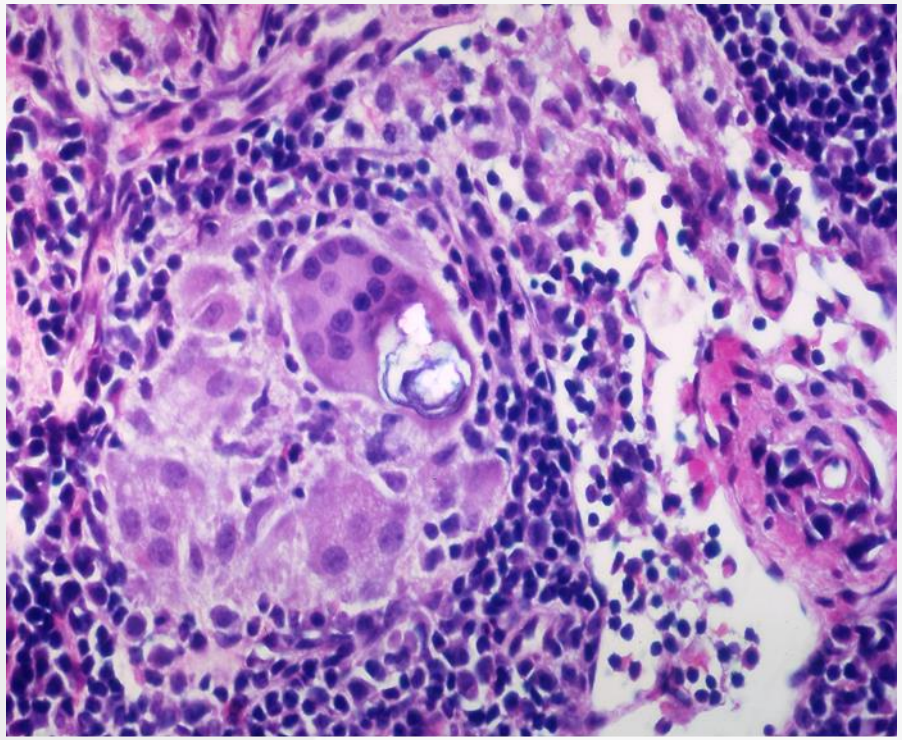
Oral Manifestations-

- There are a number of reports in the literature of oral biopsies of clinically normal tissue in patients with proven sarcoidosis that revealed lesions, which were microscopically consistent with the disease.
- Lesions on the lips were manifested clinically as small, papular nodules or plaques, or resembled herpetic lesions or ‘fever blisters’.
- On the palate and buccal mucosa, the lesions have been described as bleb-like, containing a clear yellowish fluid, or as solid nodules. It also appears that sarcoid may produce diffuse destruction of the bone.



Histologic Features-

- Sarcoid lesions closely resemble pro- liferative noncaseating nodules of tuberculosis, and the differ- ential diagnosis is frequently difficult to establish.
- Nests of epithelioid cells, with multinucleated giant cells, are one of the chief microscopic features of the fi- brous granulomatous nodules.
- These granulomas also contain T and B cells, as well as various immunoglobulins that can be identified by appropriate immunofluorescence.
- Caseation and necrosis do not occur, although the granuloma ultimately transforms into a solid, amorphous, eosinophilic, and hyaline mass as it ages.



Wegener’s Granulomatosis

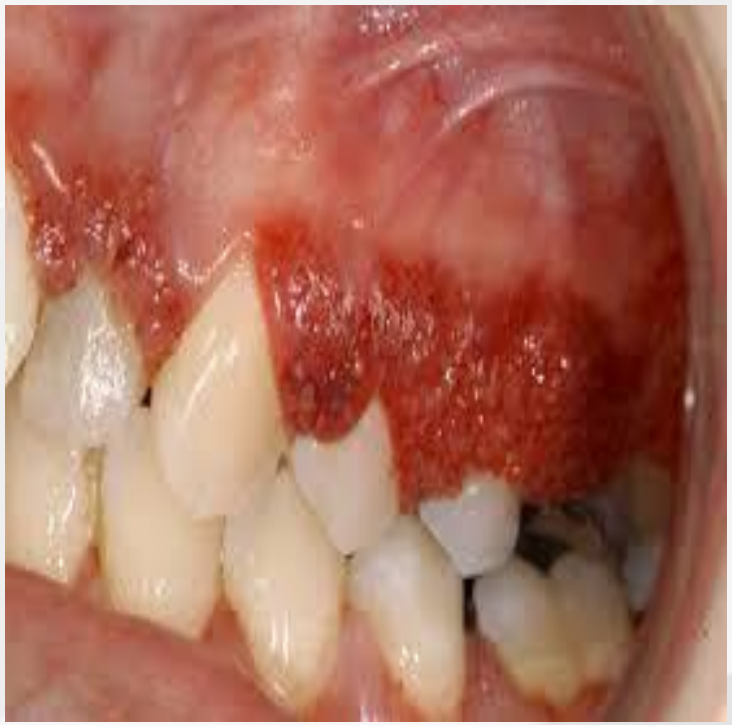
- Wegener’s granulomatosis is a disease of unknown etiology, which basically involves the vascular, renal, and respiratory systems.
- It involves the nose, paranasal air sinuses, lower respiratory tract, gut, joints, nervous system, and kidneys. Involvement of the kidney is the common cause of death.
- Wegener’s granulomatosis is due to the formation of anti-neutrophil cytoplasmic antibody formation.
- Organs involved in Wegener’s granuloma exhibit inflammation with granuloma formation against a nonspecific inflammatory background.

Clinical Features-

- Wegener's granulomatosis may occur at any age, from infants to the very elderly, although the majority of cases are in the fourth and fifth decades of life.
- There is a sight predilection for occurrence in males.
- It is characterized clinically by the development of rhinitis, sinusitis, and otitis or ocular symptoms.
- The patient soon develops a cough and hemoptysis as well as fever and joint pain.
- Hemorrhagic or vesicular skin lesions are also commonly present.
- Granulomatous lesions of the lungs are found on the chest radiograph, while the glomerulonephritis, which develops ultimately, leads to uremia and terminal renal failure.
- In nervous system, sensory neuropathy may be an occasional finding.

Oral Manifestations-

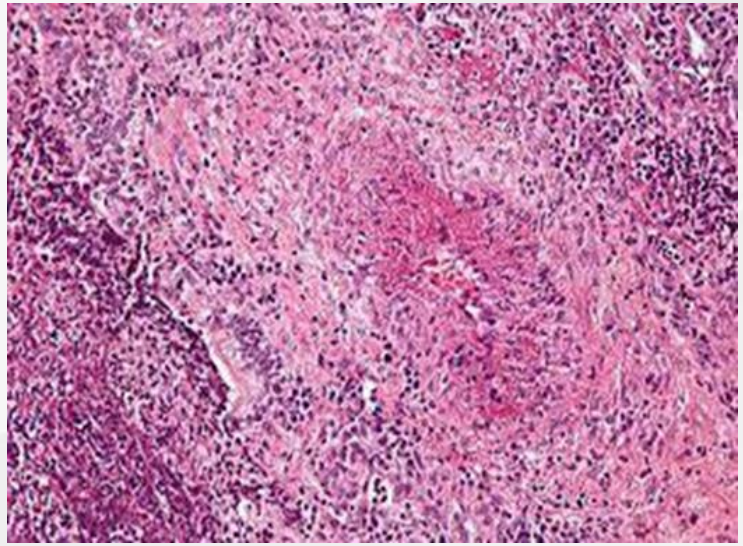
- Involvement of the oral cavity occurs with considerable frequency in Wegener's granulomatosis.
- It is termed as **strawberry gingivitis.**
- The gingival lesions may be ulcerations, friable granular lesions, or simply enlargements of the gingiva.
- The inflammatory process starts in the interdental papilla and spreads rapidly to the periodontal structure and leads to bone loss and tooth mobility.
- Other lesions may occur ulceration of the palate by extension of the disease from the nose, where destruction of the nasal septum may develop; also occurring are small ulcerations resembling aphthae, diffuse ulcerative stomatitis, spontaneous exfoliation of teeth, and failure of tooth sockets to heal following extraction.

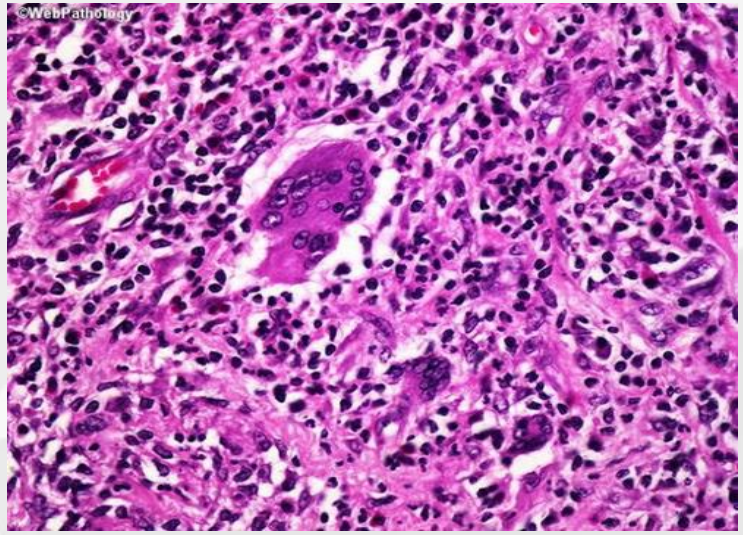


Histologic Findings-

- Wegener’s granulomatosis presents a pattern of mixed inflammation centered around the blood vessels.
- The lesions in the upper respiratory tract and lungs consist of giant cell necrotizing granulomatous lesions show- ing vasculitis.
- Oral biopsy specimens show pseudoepithelio- matous hyperplasia and subepithelial abscesses.

The gingival and other lesions show a nonspecific granulomatous process with scattered giant cells.





Treatment

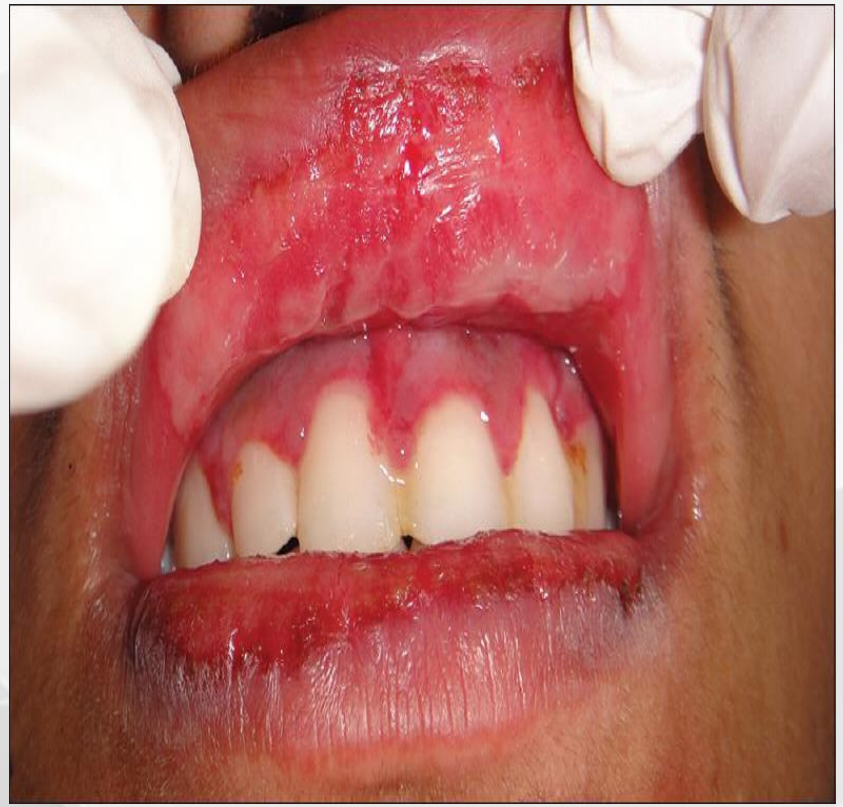
- The majority of cases of Wegener’s granuloma- tosis formerly terminated fatally. The mean survival rate of untreated patients is five years.

- However, cytotoxic agents, especially cyclophosphamide, and prednisone have provid- ed a good prognosis for these patients, with many known long-term remissions.

Contact Stomatitis and Dermatitis

(Stomatitis and dermatitis venenata)

- A contact allergy is a type of reaction in which a lesion of the skin or mucous membrane occurs at a localized site after repeated contact with the causative agent.
- These causative agents are chemical in nature (haptens) and require conjugation with proteins to become effective.
- It is then presented to the T lymphocytes for sensitization and production of IgE with specific receptors.

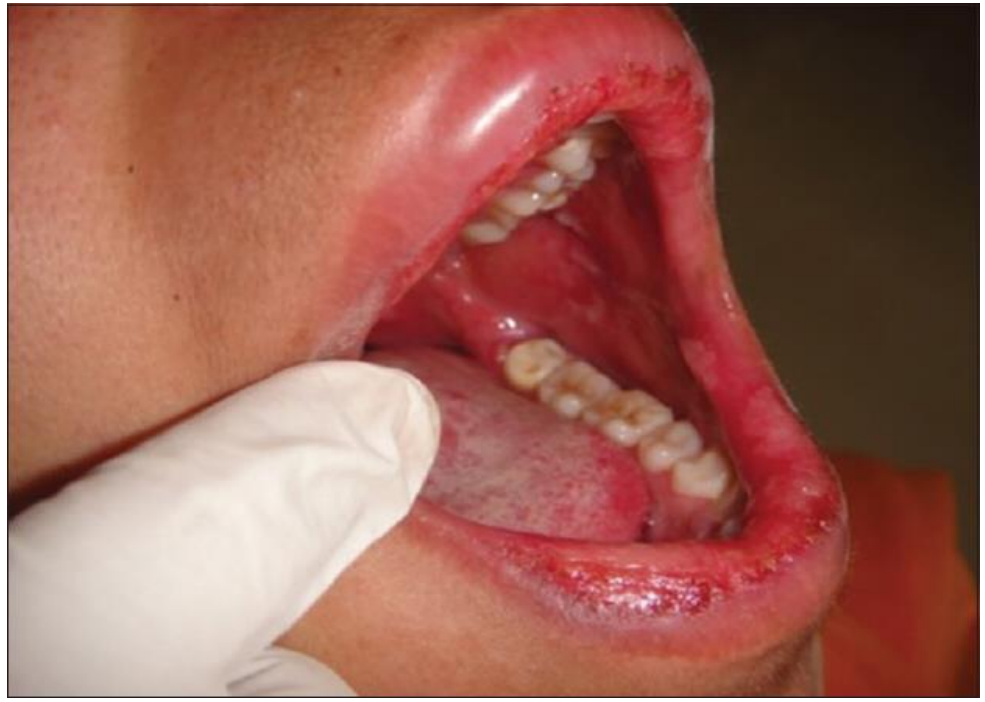


These may be classified as follows:

1. **Dental or cosmetic preparations**
   - Dentifrices
   - Mouthwashes
   - Denture powders
   - Lipstick, candy, cough drops, chewing gum
2. **Dental materials**
   - Rubber dam
   - Vulcanite
   - Acrylic
   - Metal alloy base
3. **Dental therapeutic agents**
   - Alcohols
   - Antibiotics
   - Iodides
   - Phenols
   - Procaine
   - Volatile oils

Clinical Features-

- Contact dermatitis is manifested by the occurrence of an itching or burning sensation at the site of contact, followed shortly by the appearance of an erythema and then vesicle formation.
- After rupture of the vesicles, erosion may become extensive, and if secondary infection occurs, the lesions may be serious.
- In chronic contact, the skin may become thickened and dry.

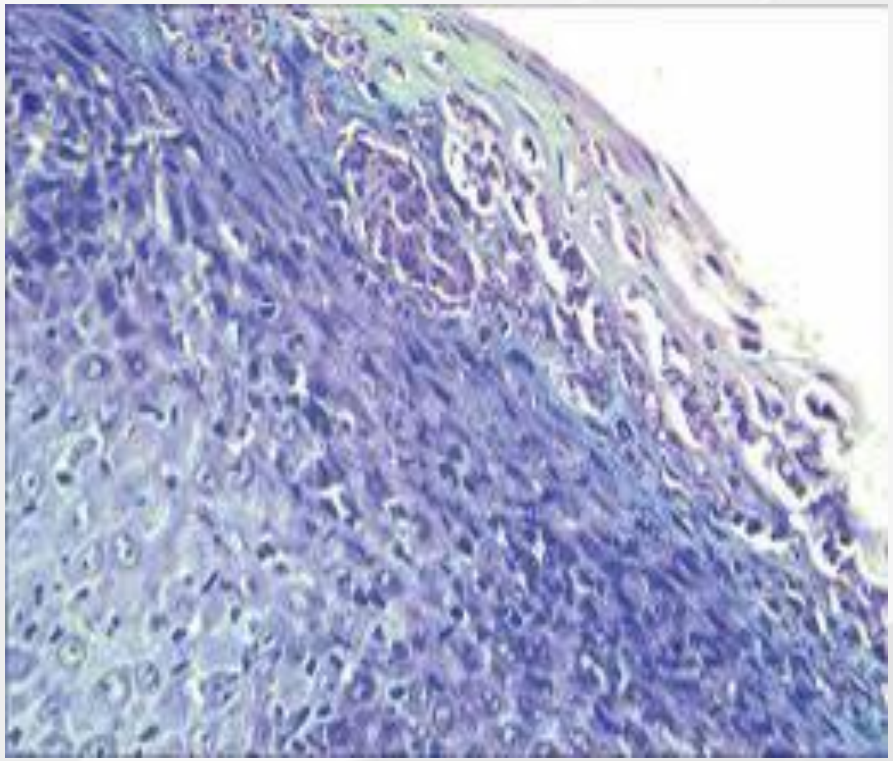


Oral Manifestations

- The tissue is uniformly bright red in all quadrants, in contrast to the plaque-induced gingivitis which is more localized and usually spares attached gingiva.
- Buccal mucosa is usually puffy and dark red, revealing engorged and ejected superficial capillaries on closer examination.
- Small vesicles may form, but these are transient and soon rupture to form small areas of erosion and ulceration, which may become extensive in some cases .
- Such swollen and edematous features subject to erosion and ulceration are more common in the lips.
- Secondary infection is particularly common.
- These features are usually accompanied by a rather severe burning sensation. Itching, stinging, tingling, and edema may also be noted.

Histologic Features-

- Intra- and inter-cellular edema of the epithelium along with vesicle formation within the epithelium or at the basement membrane is usually seen.
- Engorged and dilated blood vessels are seen in the connective tissue against a background of edema and an infiltrate of lymphocytes and plasma cells.
- Increased number of eosinophils is a common finding in allergic reactions.



Diagnosis-

- Patch test may be a useful investigation to identify the causative agent.

Treatment and Prognosis-

- The only treatment for contact dermatitis or stomatitis consists in discontinuing all contact with the offending material.

- When this is done, there is usually prompt remission of all lesions.

Lichenoid Reaction (Lichenoid mucositis, lichenoid drug reaction, lichenoid lesions)

- Lichenoid reactions (LR) represent a group of lesions similar to lichen planus clinically and histologically. These may involve skin or oral mucosa.
- Etiology. The exact mechanism of the development of lichenoid reaction is not known, but a series of triggering factors, such as dental restorative materials, graft-versus-host disease, a broad range of drugs, flavoring agents, and tobacco chewing are identified in the causation of LR.
- Drugs such as antimalarials, non-steroidal anti-inflammatory drugs, antihypertensive agents, oral hypoglycemics, and beta blockers were reported to be associated with LR.
- Dental restorative materials such as silver amalgam, gold, cobalt, palladium, chromium and epoxy resins, preservatives and flavoring agents commonly used in foods and dentifrices also trigger LR.

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Lichenoid lesions can take many months or longer to resolve.

Clinical Features.

- They are present as reticular, erythema- tous, erosive lesions or ulcerations, with whitish streak similar to that of Wickham's striae of lichen planus.

- Clinical manifes- tations of LR are very much similar to that of lichen planus.

- An important factor which distinguishes LR from lichen pla- nus is its atypical location and absence of bilateral occurrence.

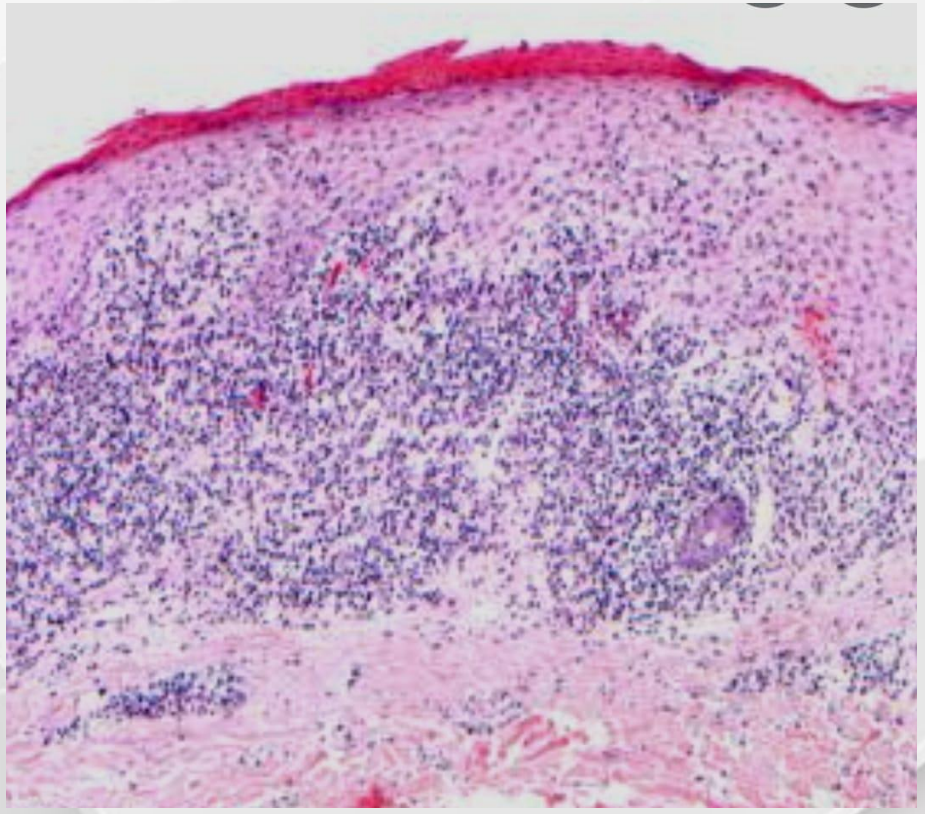
Diagnosis

- There is no specific test for the diagnosis of LR. The widely accepted criterion is based on the observation of disappearance of the lesions after withdrawal of triggering agent and recurrence of the lesions when they are reintroduced.

Histologic Features.

- Though histologically LR has superfi- cial resemblance to lichen planus there are notable differences.

- The inflammatory infiltrate is diffuse and extends deeper into the lamina propria unlike the sharp band of infiltrate seen in lichen planus.



- Inflammatory infiltrate consists of plasma cells and eosinophils in addition to lymphocytes.

- Increased numbers of colloid or Civatte bodies may be present in LR.

- A perivascular chronic inflammatory cell infiltrate can be seen in drug related lichenoid lesions, which is not commonly found in lichen planus.

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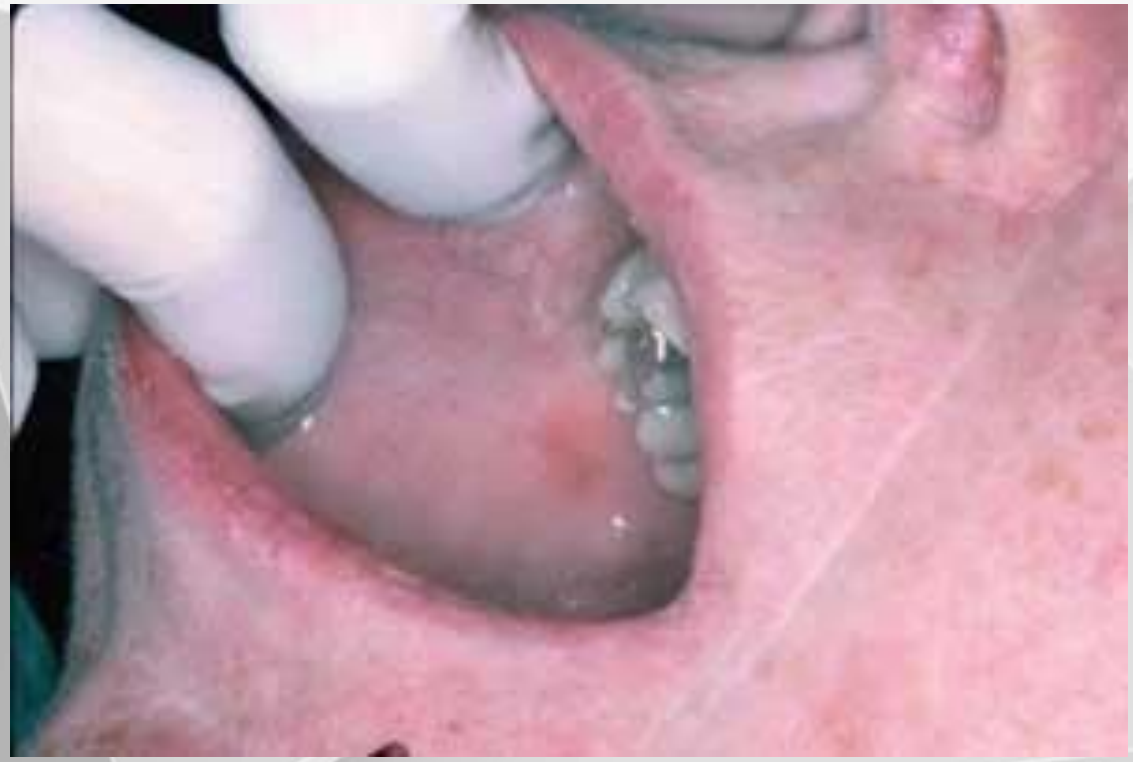
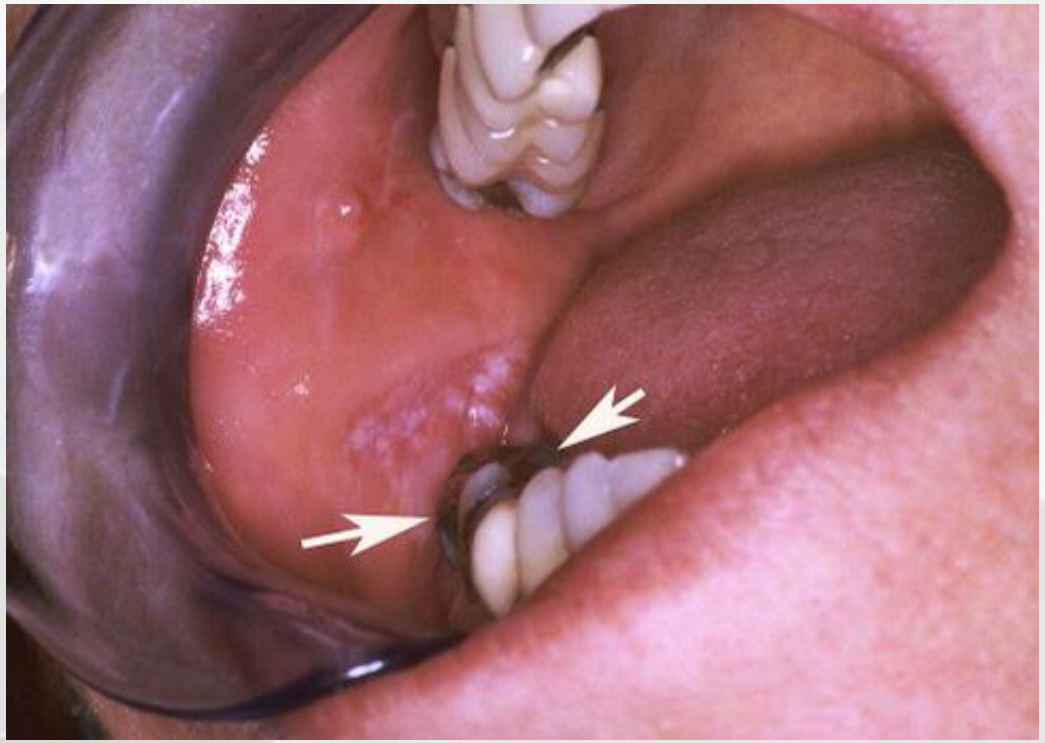
- Epithelial dysplasia associated with a band-like inflammatory infiltrate which on low-power can mimic lichen planus and is known as lichenoid dysplasia, and which may be seen in proliferative verrucous leukoplakia (PVL), an unusual form of leukoplakia, shares some demo- graphic and clinical similarities with lichen planus. PVL oc- curs most commonly in older female patients and is not as- sociated with tobacco usage.

Treatment and Prognosis

- Identification and elimination of the triggering factors play a major role in the management of LR





Thank You