Granulomatous Diseases of head and neck
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**Definition of Granuloma:**

**Granuloma** is a small, 0.5-2.0 mm collections of modified macrophages called “epithelioid cells” usually surrounded by a rim of lymphocytes. (Robbins 4th edition)

**Granuloma** is a focal area of Granulomatous inflammation. It consists of a microscopic aggregation of macrophages that are transformed into epithelium like cells surrounded by a collar of mononuclear leukocytes, principally lymphocytes & occasionally plasma cells. (Robbins 6th edition)

Turk (1971) defined a **Granuloma** as a collection of cells of the macrophages-histiocyte series with or without the admixture of other inflammatory cells.

**Granuloma** is defined as a chronic inflammatory reaction containing a preponderance of cells of the monocyte series arranged in compact masses

"A **Granuloma** is a compact (organized) collection of mature mononuclear phagocytes (macrophages and/or epithelioid cells) which may or may not be accompanied by accessory features such as necrosis or the infiltration of other inflammatory leukocytes (Adams DO. The granulomatous inflammatory response. Am J Pathol 1976:84:163-192)
Granuloma

- Low turn over Granuloma
- High turn over Granuloma

Immune Granuloma

Non-Immune Granuloma

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Pathophysiology
Of Granuloma formation
Morphological types of Granulomatous inflammation:

- **Diffuse Granulomatous reaction**: Lepromatous leprosy
- **Tuberculoid Granulomatous reaction**:
  - Non –Caseating Tuberculoid reaction
    - Sarcoidosis, Crohn’s Disease, Lupus Vulgaris, and Tuberculoid leprosy
  - Caseating Tuberculoid reaction
    - Tuberculosis
  - Suppurative tuberculoid reaction
    - Small abscesses filled with PMN
    - Surrounded by epithelioid cells
    - Lymphohgranuloma venerum, Yersinia Pseudotuberculosis, Sporitrichosis and Cat Scratch Disease.
# Causes Of Granulomatous Diseases:

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<td><em>Mycobacteria</em> E.g. T.B., Leprosy, Atypical mycobacteria, Many types of Fungi, Parasties, Larvae, Eggs &amp; Worms, Syphilis</td>
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<td>Foreign Bodies</td>
<td>Endogeneous E.g. Keratin, necrotic bone, cholesterol crystals, sodium urate</td>
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<td>Drugs</td>
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Granulomatous diseases of Head & neck can be classified as:

- Infectious
  - Fungal
  - Parasitic
  - Bacterial
- Foreign Body
  - Gout
  - Cholesterol Granuloma
  - Cocaine usage
- Unknown
  - Sarcoidosis
- Autoimmune & Vasculitis Disease
  - Wegener’s Granulomatosis
  - Orofacial Granulomatosis
  - Crohn’s Disease
- X-linked
  - Chronic Granulomatous Inflammation

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• **Fungal**
  - Histoplasma capsulatum & H. duboisi
  - Blastomycosis deramatis & Paracoccidioidomycosis brasiliensis
  - Phycomysis
  - Aspergillus fumigatus
  - Candida albicans
  - Rhinosporidiosis seeberi
  - Coccidiodes immitis
  - Cryptococcus neoformans

• **Parasitic**
  - Leishmaniasis
  - Myiasis
  - Toxoplasma gondii

• **Bacterial**
  - Mycobacterium tuberculosis
  - Nontuberculous mycobacterial infection
  - Mycobacterium leprae
  - Cat scratch disease
  - Actinomycosis
  - Syphilis
  - Rhinoscleroma

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Mycobacteria tuberculosis:

- Aerobic slender, non motile, non capsulated, non sporing, rod shaped organism 2-5 µ in length.
- Complex fatty substance in their wall – ZN staining – bright red

Auramine and rhodamine dyes are also helpful to identify the organisms by fluorescence.
Clinical and radiographic features:

- Primary tuberculosis is usually asymptomatic—occasionally fever & pleural effusion is seen

- Low grade fever malaise, anorexia, weight loss, & night sweats

- Hemoptysis, chest pain

- Wasting syndrome.....called as CONSUMPTION.

EXTRA PULMONARY TB:
  - In AIDS pt. 50% will have extra pulmonary TB.
  - Any organ can get affected
  - Skin- *lupus vulgaris*

- Most common extra pulmonary sites of head and neck are the cervical lymph nodes followed by the larynx and middle ear.
  - Much less common sites include the nasal cavity, nasopharynx, oral cavity, parotid gland, esophagus & spine.
**ORAL lesions:**

- Uncommon, appear as chronic painless ulcer, less frequently include nodular, granular or rarely firm leukoplakic patch.

0.5 -1.5% prevalence of oral lesions.

**Primary TB Lesions** seen on gingiva, mucobuccal fold and areas of inflammation adjacent to teeth or in a extraction sites

**Secondary TB lesions** seen most commonly on tongue, palate and lips

Tuberculous osteomyelitis has been reported in the jaws and appear as ill defined areas of radiolucency

Typical Tuberculous ulcer is an irregular lesion with ragged, undermined edges, minimal induration, and often with yellowish granular base.

**Sentinel tubercles**-tiny small nodules
**Scrofula:**
Enlargement of the oropharyngeal lymphoid tissues and cervical lymph nodes.
Microscopically:

Fig. 17.1 Tuberculosis: unlike most other granulomatous diseases there is deep undermining ulceration, particularly of the dorsum of the tongue or, less often, of the lips with multiple giant cell granulomas (see also Fig. 13.16).
Fig. 17.2 Tuberculosis: multiple Langhans giant cells, sometimes with caseation, within the granulomas are suggestive of tuberculosis.
Diagnosis:

Mantoux test (TUBERCULIN SKIN TEST)

Special mycobacterial stains and culture of the infected sputum or tissue

PCR
Nontuberculosis mycobacterial infections may also present as granulomatous lesions in the head and neck region. Non-TB mycobacterium are *M. kansaii*, *M. scrofulaceum*, *M. avium- intracellualaris*, *M. gordonii*, and *M. fortuitum*. Children are most frequently infected with corneal ulceration in the head and neck region. Following ocular involvement is cervical lymphadenopathy (*scrofula*), typically unilateral within the anterior cervical, preauricular, and submandibular regions.
Diagnosis

By excisional biopsy of the involved lymph node with acid fast bacilli culture. Acid fast staining of the sample for bacilli will give the presumptive diagnosis.

Treatment consists of antibiotics (i.e. isoniazid, rifampin, ethambutol, sulfonamide, fluoroquinolones) that are sensitive for the particular organism.
Leprosy:

*M. Leprae*

Requires cool host body

Transmission from nasal secretions

Oral involvement in leprosy compared to the map of the local temperature

**CLINICAL PRESENTATION:**

**Tuberculoid leprosy**
- high immunity
- Localized disease
- Organisms are not found in skin
- Lepromin test is positive

**Lepromatous leprosy**
- low immunity
- Numerous organisms in the tissue
- Diffuse disease
- Lepromin test is negative
Active disease progresses through stages of invasion, proliferation, ulceration and resolution with fibrosis

Incubation period-2-5 years for tuberculoid type
8-12 years for lepromatous variant

**Clinical features:**

**Leprosy**

*Paucibacillary* Tuberculoid pattern, small number of well-circumscribed, hypopigmented skin lesions
Nerve involvement, Anesthesia of skin, loss of sweating
ORAL LESIONS ARE RARE

*Multibacillary* Lepromatous pattern
Begins slowly, numerous ill defined, hypopigmented macules or papules on the skin
Face is the common site of involvement – *Leonine faceis*

Hair, including the eye brows and lashes often are lost
Nerve involvement
Decreased touch sensitivity to touch, pain, temperature

Nasal involvement leads in nose bleeds, stuffiness and a loss of the sense of smell

Hard tissues of the floor, septum and bridge of the nose may be affected. Collapse of the nose is considered pathognomonic

**Oral lesions - 19 – 60%**
Air cooled sites are more frequent: hard palate, soft palate, labial maxillary gingiva, tongue, lips, buccal maxillary gingiva, labial mandible gingiva & buccal mucosa
Affected soft tissue appears as 

YELLOWISH TO RED, SESSILE, FIRM, ENLARGING PAPULES THAT DEVELOP ULCERATION AND NECROSIS FOLLOWED BY ATTEMPTED HEALING BY SECONDARY INTENTION 

Complete loss of uvula & fixation of the soft palate may occur

Lingual lesions primarily occur in the anterior third & often begin as areas of erosion

Infection of the lip results in **MACROCHELIA**
Fig. 17.3 Leprosy (lepromatous type): unlike tuberculosis, nodules can form on the lips or tongue; these may later break down to form ulcers.

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**Facies leprosa:** Triad- atrophy of the anterior nasal spine, atrophy of the anterior maxillary gingiva and endonasal inflammatory changes

**MAXILARY INVOLVEMENT CAUSES:**
- Enamel hypoplasia of the developing teeth & tapering roots
- Dental pulpal involvement: pulpal necrosis, obvious red discoloration of the crown
- Granulomatous involvement of the nasal cavity can lead to perforation in the oral cavity
- Facial & trigeminal involvement also seen.
Histopathology

**Paucicellular**
- Tuberculoid pattern
- Paucity of organisms
- FITE METHOD

**Multicellular**
- Lepromatous pattern
- Abundance of organisms
- AFB METHOD
Fig. 17.4 Leprosy: in the tuberculoid form, multiple compact non-caseating granulomas are present in the corium.
Diagnosis:

Clinical presentation

**AFB stain**

The organism can not be cultivated on artificial media but *M. leprae* can be identified by using molecular biology techniques.

There is no reliable test to determine whether a person has been exposed to *M. Leprae* without developing the disease.
Cat Scratch Disease:

- Infectious disorder that begins in the skin but classically spreads to the adjacent lymph nodes.
- Most common cause of chronic regional lymphadenopathy in children.

*Rochalimae henselae / Bartonella henselae*
Or
*Afipia felis*

Age: under 21
Papular/ pustule that develops in 3- 14 days along the line of scratch

Enlargement of lymph node

Fever & malaise

**Unusual Presentation:**

Intraoral mass in the buccal mucosa when lymphoid aggregates becomes involved from an adjacent Cutaneous primary site.

Scratch in the preauricular area may localize in the parotid lymphoid tissue And cause significant parotid pain or even temporary facial paralysis.

Primary lesions adjacent to the eye can result in conjuctival granuloma associated with preauricular lymphadenopathy (oculoglandular syndrome of Parinaud)
Enlarged lymph nodes as a result of significant cortical hyperplasia, which classically contains areas of stellate suppurative necrosis surrounded by a band of histiocytes and neutrophils.

In some cases significant areas of necrosis are absent but areas of karyorrhexis are present around proliferations of plump vascular channels that often exhibit thickened eosinophilic walls.

Warthin starry method

Brown hopps method of gram staining
Fig. 17.6 Cat-scratch disease: (upper) low power view of an involved lymph node shows the foci of necrosis within epithelioid granulomas; (lower) at higher power, a granuloma with central necrosis has appearances somewhat similar to those of one of the deep mycoses.
Diagnosis:

Serological tests: Antibodies to Bartonella henselae
ELISA for IgM antibodies to organism
PCR

BEFORE AVAILIBILTY OF SEROLOGICAL TESTS FOLOWING CRITERIA WAS USED: ¾
1. Contact with cat, presence of a scratch or a primary dermal or ocular lesions.
2. Positive hanger rose skin test....no longer used
3. Negative results for the causes of lymphadenopathy
4. Characteristic pathologic findings of infected tissue.

Self limiting disease
Syphilis:

- Treponema pallidium

Infection

2-6 weeks

Primary

1-3 months

Secondary

1-3 months

Latent

2-50 years

Lifetime Latency 70% 30%

Tertiary

Gumma

Central Nervous System

Cardiovascular System

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Primary stage: Papular lesions which develop a central ulceration. Oral cavity is the most common extra genital site…lip, tongue, palate, gingiva, palate, tonsils

Painless clean based ulceration or rarely as a vascular proliferation resembling a pyogenic granuloma

Regional lymphadenopathy bilaterally
Secondary stage:

Painless lymphadenopathy, sore throat, malaise, headache, weight loss, fever and musculoskeletal pain

**CONSISTENT SIGN:** Diffuse, painless, maculopapular Cutaneous rash, which is wide spread and can even affect the palmar plantar areas
30% - focal areas of intense exocytosis & spongiosis of the oral mucosa, leading to zones of sensitive whitish mucosa known as **MUCOUS PATCHES**

Can occur anywhere in oral cavity ..most commonly seen on tongue, lip, buccal mucosa and palate

Papillary lesions – **condyloma lata**
Lues Maligna – Prodromal symptoms of fever, headache, and myalgia, followed by formation of necrotic ulcerations which commonly involve the face & scalp

**Tertiary stage:**

The organisms spread to various organs causing lesions or gummas
Less significant, but more characteristic, are scattered foci of Granulomatous inflammation, which may affect the skin, mucosa, soft tissue, bones & internal organs. This active site of Granulomatous inflammation is known as **GUMMA**

The tongue may be involved diffusely with gummata and appear large, lobulated, and irregularly shaped....

**INTERSTITIAL GLOSSITIS** (Contracture of the lingual musculature after healing of gummases)

Diffuse atrophy & loss of the dorsal tongue papillae produce a condition called **luetic glossitis**

**luetic glossitis** - NOT PRECANCEROUS
Congenital Syphilis:

- Hutchinson’s teeth
- Ocular interstitial keratitis
- Eighth nerve deafness
**Histopathology**

**Primary and secondary syphilis:**

The surface epithelium is ulcerated in primary, pseudoepitheliomatous in secondary.

**Lamina Propria:** shows an increase in the no. of vascular channels and an intense chronic inflammatory infiltrate composed of **lymphocytes & plasma cells** in a perivascular pattern.

Warthin starry-CORKSCREW SPIROCHAETAL

**Direct Fluorescence Antibody Testing**

**Tertiary lesions:**

Ulceration, peripheral pseudoepitheliomatous hyperplasia, foci of Granulomatous inflammation with well circumscribed collection of histiocytes & multinucleated giant cells.

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Syphilitic lymphadenitis
Cervical lymph node biopsied from a febrile man with a high titer of TPHA

The enlarged node is multifocally replaced by epithelioid granulomas (HE, low power). No caseous necrosis is seen. The features represent tertiary syphilis forming gumma.

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Formation of epithelioid granuloma with Langhans-type giant cells is evident histologically (HE). In this case, the diagnosis of "granulomatous lymphadenitis" is unsatisfactory. Etiological seeking is important, particularly when the possibility of syphilis is clinically not suspected.
A few spiral pathogens are identified in the granulomatous lesion by immunostaining for *Treponema pallidum* antigens, confirming the diagnosis of tertiary syphilis. Warthin-Starry's silver was negative.

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Diagnosis:

Dark field examination of a smear of the exudate of an active lesion

False positive results are possible

Specific immunofluorescent antibody or serologic tests

VDRL, Rapid Plasma Reagin (RPR)

ABOVE TESTS ARE NON SPECIFIC

HIGHLY SPECIFIC TESTS INCLUDE:

Fluorescent Treponema Antibody Resorption (FTA-ABS)
Treponema Pallidium Haemagglutination assays (TPHA)
Rhinoscleroma:

- *Klebsiella rhinoscleromatis*  
  - Central America & Eastern Europe  
  - Mode of transmission not known

**THREE STAGES:**

- **Catarrhal Stage**: Prolonged purulent rhinorrhea  
  (honeycombed color)

- **Granulomatous stage**: Characterized by small,  
  nodular masses in the upper airway which later coalesce

- **Sclerotic stage**: Dense fibrosis that causes stenosis of the nose,  
  larynx, and tracheobronchial tree.

The proliferative masses may produce the  
configuration as the “HEBRA NOSE” which is typical of disease  

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Oral lesions: Proliferative granuloma,
Anesthesia of the soft palate & enlargement of the uvula

Demonstrating the existence of the organism in vacuolated histiocytes can be useful in diagnosis.
An indolent suppurative infection caused by an anaerobic or microaerophilic organism.

Infection follows after aspiration of the *Actinomyces* organism into the lung, or contact of the organism with damaged mucosa (i.e. poor dental hygiene, dental abscess).
Pathologically, the agent grows in characteristic grains.

The infectious process is walled off by the granulomatous inflammatory process with extensive fibrosis demonstrated on histological studies.
Clinical features:

Cervicofacial actinomycosis typically presents as a red, indurated, non tender subcutaneous mass in the anterior cervical triangle or submandibular region. The overlying skin may have a purplish discoloration.

There may be several draining sinuses present (61% of patients).

In addition, 57-89% of patients report fever, while other symptoms include weight loss, malaise, nausea, vomiting, and sweating.
Demonstration of characteristic sulfur granules on microscopic examination provides the diagnosis with confirmation by culture.

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Foreign body granulomas:

The urate crystals in *gout* incite Granulomatous lesions

*Histologically*, the crystals are surrounded by a fibroblasts, plasma cells, macrophages, and foreign body giant cells. The resulting lesion is referred to as a tophi.

*Throughout the body, helix or antihelix of the ear*

Tophi may ulcerate and extrude a material that is rich in monosodium urate crystals. Examination under polarizing microscopy for urate crystals aids in distinguishing this from other causes of subcutaneous nodules.

*Gout also produces an arthritis type picture*

Symptoms from this involvement include throat pain, hoarseness, and dysphonia.
Cholesterol granulomas are usually found in the pneumatized area of the temporal bone or the paranasal sinuses. For these granulomas to form, there is a predisposing lack of aeration to the site. Cholesterol precipitates in the areas of cell breakdown (erythrocytes, mucosa) with a resulting foreign body reaction.

Topical nasal usage of *cocaine* may produce ulcerative granulomas which erode the nasal septum, soft palate and/or nasopharyngeal mucosa. *Staph aureus* propagates the ulcer in most cases.
Sarcoidosis:

Multisystem granulomatous disorder of unknown cause

Improper degradation of antiseptic material with formation of non-Caseating granulomatous inflammation.

Nature of antigen is unknown

PCR, DNA & RNA *in situ hybridization* have detected increased levels of mycobacterial DNA in bronchoalveolar lavage material from patient with Sarcoidosis.

The inappropriate defense response may result from prolonged or heavy Antigenic exposure an immunodysregulation (genetic or secondary to other factors ) that prevents an adequate cell - mediated response, a defective regulation of the initial immune response, or a combination of all three factors
Clinical Features

Worldwide distribution

**North American Blacks** are 10 – 17 times more frequently than whites

Female predilection

20-40 years

Sarcoidosis most commonly appears acutely over a period of days to weeks, and the symptoms are variable

**Common symptoms:** Dyspnea, dry cough, chest pain, fever, malaise, fatigue, arthralgia, and weight loss

20% patients – NO SYMPTOMS discovered on routine CXR
Although any organ may be affected, the lungs, lymph nodes, skin, eyes & salivary glands are prominent sites.

Lymphoid tissue is involved in almost all cases.

Mediastinal & Paratracheal lymph nodes are involved.

CXR- bilateral hilar lymphadenopathy

(approx. 90% patients reveal an abnormal CXR some time during the course of disease)
Cutaneous Manifestations occur about 25%
-Chronic, Violaceous, Indurated lesions

*LUPUS PERNIO* – Nose, ears, lips & face.
Symmetric, elevated, Indurated, purplish plaques are commonly seen on the limbs, back and buttocks.

Scattered, Non-specific, tender erythematous nodules known as **erythema nodosum** (frequently occur on the lower legs)

Ocular involvement - 25%
- Anterior uveitis
- Lesions of conjunctiva & Retina may occur
  - Keratoconjunctivitis sicca

Salivary glands can be enlarged with **Xerostomia**
Salivary glands can be Enlarged (mimics sjogrens syndrome)

Salivary gland biopsy
Although lymphoid, pulmonary, cutaneous, and ocular lesions are most common, virtually any organ system may be affected.

Other potential skin include the Endocrine system, Gastrointestinal tract, Heart, kidneys, Liver, Nervous system & Spleen.

Intra-osseous lesions may occur and most commonly involve the Phalanges, Metacarpals, and Metatarsals.

Less frequently, the skull, nasal bones, ribs & vertebrae are affected.
TWO DISTINCT SYNDROMES ARE ASSOCIATED WITH ACUTE SARCOIDOSIS:

LOFGREN’S SYNDROME: Erythema nodusum, Bilateral hilar lymphadenopathy & Arthralgia


Salivary gland & Lymph node involvement are excluded, clinically evident oral manifestation in Sarcoidosis are uncommon.
- Submucosal mass, an isolated papule or an area of granularity

- Mucosal lesions may be normal in color, brownish-red, violaceous or hyperkeratotic

Buccal mucosa > gingiva> lips> floor of mouth> tongue> palate

- Intraosseous lesions affect either jaw & represent approx. ¼ of all reported intra oral cases
  – ILL DEFINED RADIOLUCENCIES
-Tightly clustered aggregates of epithelioid histiocytes are present, with a surrounding rim of lymphocytes, intermixed with histiocytes are scattered Langhan’s or foreign body type giant cells.

-The granulomas often contain laminated basophilic calcification, known as “Schaumann Bodies” also called as “Chonhoidal bodies” or stellate inclusions known as “Asteroid bodies”. HAMAZAKI-WESENBERG (H-W) BODIES also seen. The pigment appears to be lipofuscin. Ultrastructural studies have shown that H-W bodies are giant lysosomes and residual bodies.
Fig. 17.7 Sarcoidosis: involvement of lymphoid tissue by many compact granulomas is typical of the disease.

Fig. 17.8 Sarcoidosis: a typical compact granuloma, formed by histiocytes (epithelioid cells) and surrounded by a dense lymphocytic infiltrate.
Fig. 17.9 Sarcoidosis: inclusions within giant cells are sometimes seen but are not of diagnostic significance.
Fig. 17.11 Sarcoidosis: this gingival papilla shows typical granulomas and the surrounding lymphocytic infiltrate, but confirmation of the diagnosis depends on the systemic findings.
Fig. 17.12 Sarcoidosis: minor labial salivary gland showing multiple epithelioid granulomas and multinucleated giant cells.
Diagnosis:

Clinical & radiographic examination
Histopathologic findings
Negative stains with both special stains & culture
High angiotensin - converting enzyme levels
Pulmonary involvement

Lab investigation:
Eosinophilia, Leukopenia, anemia, thrombocytopenia,
high serum alkaline phosphatase level, high ESR
high serum calcium conc., High urinary calcium level.

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Skin test:

KVEIM Test
Orofacial Granulomatosis

Group of related conditions characterized by granulomatous inflammation in the oral & maxillofacial region.

Diagnosis by exclusion

Similar Histopathologic & clinical picture:
- foreign body granulomas,
- chronic granulomatous disease
- Crohn's disease
- Sarcoidosis
- Mycobacterial infections.
First described by Hubschmann (1894), Mart (1859), Luscher (1949)

Weisenfeld et al 1985-Specific clinical & pathologic entity

May occur in isolated form or in association with other disease.

Melkersson rosenthal syndrome
Cheilitis granulomataosa of Miescher

Analogous to apthous ulcer

After initial diagnosis, patient is evaluated for several systemic diseases
Clinical features:

Most common site is lip - non tender persistent swelling

Rarely superficial amber colored vesicles are found resembling lymphangiomas

Gingival erythema, mucosal erythema, erosions & associated oral discomfort
**Dysgeusia**- anterior 2/3 of the tongue

Swelling of the upper part of the face may be seen

**Other symptoms**- abnormal lacrimation, sweating, migraine-like headache, hyper or hypo salivation, hyperacusis, blepharospasm

Cobble stone appearance of buccal mucosa

Linear hyperplastic folds in the mucobuccal fold, with linear ulcerations

Palate may have papules or large areas of hyperplastic tissue
Causes:

- 12-60% cases are atopic, others are allergic to food additives- cinnamonaldehyde, carvone, coca, carmosine, sun yellow dye, monosodium glutamate

- **Hornstein** - polyetiologic where a hereditary or acquired predisposition to a functional disturbance of the autonomic nervous system results from allergic response to non-specific circulating antigen.

- **Henry** – alteration in CD4/CD8 T-cell subset abnormality in association with crohn’s disease & sarcoidosis

- **Ivanyi et al** – high titer of mycobacterium stress protein antigen msp65
Histopathology

Edema in the superficial lamina propria, dilatation of lymphatic vessels & scattered lymphocytes seen diffusely & in clusters

Fibrosis

Scattered areas of noncaseating granulomatous inflammation - lymphocytes, epithelioid histiocytes with or without multinucleated giant cells.

Granulomas appear to cluster around scattered vessels and are not as well formed as in sarcoidosis.
Diagnosis:

Histopathologic demonstration of granulomatous inflammation

Negative stain and culture for fungi

No foreign material

Considering all diseases in differential diagnosis

When no cause is found the diagnosis of Orofacial Granulomatosis is given
Wegener’s Granulomatosis:

Well recognized, uncommon, unknown cause.

Necrotizing granulomatous lesions of respiratory tract, necrotizing glomerulonephritis & systemic vasculitis of small arteries & veins.

**Cause**

An abnormal immune response to a non-specific infection
Or an aberrant hypersensitivity response to an inhaled antigen.

A possible hereditary predisposition.

**Clinical features:**

Wide range (average 40 years)
no sex predilection
Prevalence 3/100,000.
can involve almost every organ of the body

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Wegener’s Granulomatosis:

Classic
- upper & lower respiratory tract
- renal involvement develops rapidly

Limited
- only respiratory tract

Superficial
- skin & Mucosa
- Systemic Involvement slowly

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Purulent nasal drainage, chronic sinus pain, nasal ulceration, congestion, and fever are frequent findings from upper respiratory involvement.

Otitis media, sore throat, epistaxis, destruction of nasal septum (resulting in saddle nose)

Lower respiratory tract infection - ASYMPTOMATIC - dry cough, hemoptysis, dyspnea or chest pain.

**Renal involvement:**
occurs late in disease, most frequent cause of disease. Glomerulonephritis results in proteinuria & red blood cell casts.
Oral lesions:

**Strawberry gingivitis**

Buccal surfaces, localized or generalized, destruction of the underlying bone causing tooth mobility

Non specific Oral Ulcerations
Other manifestations:
Facial paralysis, labial & mucosal nodules, sinusitis-related tooth ache, arthralgia of TMJ, Jaw claudication, palatal ulceration from nasal ulceration, Oro-antral fistula & poorly healing extraction sites.

Enlargement of one or more major salivary glands
Mixed inflammation centered around the blood vessels

Transmural inflammation, heavy neutrophilic infiltration, necrosis & nuclear dust (leukocytoclastic Vasculitis)

Connective tissue shows adjacent to blood vessels

Inflammatory cellular infiltrate - variable mixture of histiocytes, lymphocytes, eosinophils and multinucleated giant cells.

Oral Biopsies:

Demonstrate PEH & sub epithelial abscesses,

Because of the paucity of large blood vessels in oral mucosa Vasculitis may not be evident

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Fig. 17.25 Wegener’s granulomatosis: (left) in this biopsy from the gingiva from the patient shown in Fig. 17.23, giant cells are prominent in an edematous stroma where there is a relatively light mixed inflammatory infiltrate which includes neutrophils; (right) prominent vasculitis in material from the depths of the palatal tissues where the vessels are larger. There is infiltration of the arterial wall by inflammatory cells, destruction of the normal architecture, and fibrinoid deposits.
Fig. 17.26 Wegener’s granulomatosis: low power view of the gingiva shows a dense mixed inflammatory infiltrate in the corium and irregular hyperplasia (erroneously described as pseudoepitheliomatous) of the overlying epithelium.
Diagnosis:
Clinical presentation
Microscopic finding of necrotizing and granulomatous Vasculitis

Radiographic evaluation of the chest & sinus is recommended to document possible involvement.

Serum creatinine & urinanalysis are used to rule out any renal involvement

**Lab marker:**
Indirect immunofluorescence for serum antibodies against cytoplasmic component of neutrophils (ANCA)
-p-ANCA
-c-ANCA..........90-95% POSITIVE IN ACUTE CASES

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Chronic Granulomatous Disease:

An uncommon hereditary disease, X-linked mode of transmission, 1957

Males

Infants, children

**Characterized by:**

Severe recurrent infections as a result of a defect of intracellular Leukocyte enzymatic function with a decreased oxidative metabolism in which there is failure to destroy certain catalase - positive microorganisms including staphylococci, enteric bacilli.

Other organisms such as streptococci & pneumococci are readily destroyed by the leukocytes.

**THE CHEMOTACTIC & PHAGOCYTIC FUNCTIONS OF THE LEUKOCYTES ARE GENERALLY IMPAIRED**

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Clinical features:

Widespread infection – lymph nodes, lung, liver, spleen, bone & skin

Eczematous lesions on the skin leading to necrosis & Granuloma formation.

Abscesses, septicemia, pneumonia, pericarditis, meningitis & osteomyelitis are but examples of various forms of this disease

Oral manifestation:

Diffuse stomatitis with or without solitary or multiple ulcerations
benign migratory glossitis
Enamel hypoplasia of permanent
Small granulomas with mononuclear histiocytes & multinucleated giant cells

Central necrosis with polymorph nuclear leukocytes may also be present.

**Diagnosis:**

NBT TEST
Crohn’s Disease

Unknown etiology

Most commonly affects the iliocaecal region causing thickening or ulceration or both.

Effects include abdominal pains, variable constipation or diarrhea & sometimes obstructional malabsorption. Oral involvement if infrequent but may precede abdominal changes.

**Oral manifestations:**
- Swelling, ulcerations-labial, Buccal, gingival
- Gingivitis
- Apthous like ulcers (persistent & deep with hyperplastic margins)
- Ridges of hyperplastic tissue
Cobblestone appearance

Fig. 17.16 Crohn’s disease: soft nodular proliferation of the oral mucosa is a typical feature and, in this case, was associated with facial swelling and intermittent diarrhea.

Fig. 17.17 Crohn’s disease: gross labial swelling and intraoral mucosal proliferation with typical histological changes led to the finding of extensive intestinal involvement.
Oral lesions typically show dilated lymphatics, focal aggregation of Lymphocytes & irregular, perivascular mononuclear cell infiltrate and in particular, loose, non caseating granulomas, with or without multinucleated giant cells in the corium, but often few in number.

The overlying epithelium may be normal or ulcerated.
Fig. 17.18 Crohn’s disease: low power view showing the mucosal proliferation responsible for the cobblestone appearances seen clinically in this disease.
Fig. 17.19 Crohn’s disease: isolated granulomas scattered at various depths in the oral tissues are a typical finding. There is also epithelial hyperplasia and a relatively light, scattered, inflammatory infiltrate.
Fig. 17.20 Crohn’s disease: (left) loose granulomas, as seen here, without a dense peripheral lymphocytic infiltrate, are generally unlike those of sarcoidosis; (right) biopsy from the patient in Fig. 17.17 shows multiple loose textured granulomas and unusually many giant cells.
Diagnosis:

Clinical presentation

Microscopic finding
Midline lethal granuloma

Unusual condition, resembling a serious infection

Idiopathic destruction of the nose, Para nasal sinuses, palate, face & pharynx.

First extensively reviewed by Stewart in 1933.

Complete lack of resistance to progress of infection

It is now recognized that many specific diseases may have the same clinical Manifestation as originally described for the midline lethal granuloma.
Clinical features:

Superficial ulceration of the palate or nasal septum - preceded by a feeling of stuffiness (bears a close resemblance to carcinoma).

Ulceration spreads from the palate to the nose and then outside the nose. The palatal, nasal and malar bones eventually get involved, undergoing necrosis & eventually sequestrate.

Destruction is a prominent feature, loss of entire palate.

Purulent discharge from eyes, nose.
Sloughing of the soft tissue of face.
Leaving a direct opening to the nosopharynx and oral cavity.

Patient ultimately dies of exhaustion or of hemorrhage if a large blood vessel is involved.

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Histopathology

Extensive necrosis with infiltration of some inflammatory cells

Diagnosis:

Typically one of exclusion
Fate of Granuloma:

• Granulomas may either involute (resolve) or undergo fibrosis.

• Emigration of cells, reversion of mature mononuclear phagocytes to less mature forms, and apoptosis play a role in involution.

• Fibrosis usually begins at the periphery of the granuloma.

Where granulomas are discrete and separate from each other the scars conform to the shapes of the pre-existing granulomas. These scars, which are usually recognizable as healed granulomas, are sometimes referred to as "tombstone lesions".
Involution of granuloma

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