GRANULOMATOUS DISEASES AFFECTING ORAL CAVITY: A REVIEW

Vela Desai and Prerna Pratik

Department of Oral Medicine and Radiology, Jaipur Dental College, Dhand, Amer, Jaipur, India.

ABSTRACT
Granulomatous diseases represents a unique form of the chronic inflammatory response. Granulomatous diseases of the oral soft & hard tissues is an uncommon occurrence but when found it presents as a definite diagnostic dilemma because of the wide variety of possible etiologic diseases & rather generic appearance of the individual lesions. This article highlights various granulomatous diseases affecting oral cavity with emphasis on oral manifestations.

Keywords: granulomatous diseases, oral mucosa,

INTRODUCTION
Granulomatous diseases have plagued humans for million years, with evidence of tuberculosis infection in Egyptians mummies & description of the syphilis has also been said to have been described by Hippocrates & was recognized as a venereal disease in the fifteenth century. In seventeenth century, the minute granules (milliary) in host tissues were noted. Robert Koch developed a method of staining & identified bacteria & was able to differentiate infectious, noninfectious granulomatous diseases. The advent of modern pathology with improved microscopic staining techniques & communication between researches spawned this new category of Granulomatous diseases in early twentieth century.¹

Tuberculosis
Common worldwide. Caused by Mycobacterium tuberculosis. Usually lungs more affected followed by other organs. Initial – primary infection followed by latent period. C/F: classified as
a) Pulmonary
b) Extra pulmonary
Pulmonary may be primary or secondary
Primary disease results from an initial infection with M tuberculosis – unexposed individuals are asymptomatic. Lesions are peripheral and localized to mid and lower lung zone accompanied by hilar or paratracheal lymphadenopathy. Most cases lesions heal spontaneously which later becomes evident with small calcified nodules [Ghon lesion]. Initial lesion enlarges, cavitates, invades and destroys bronchial walls and blood vessels. Pt may develop pulmonary effusion and progressive TB. Secondary pulmonary TB – post primary disease – endogenous reactivation of latent infection. Triggers for reactivation includes immunosuppression. Usually occurs in apical and posterior segment of upper lung lobes – high O₂ tension favours mycobacterial growth. Secondary pulmonary TB – fever, night sweats, weight loss, anorexia, general malaise and weakness. Cough develops eventually – non productive – purulent sputum – blood streaked. Common sites of pulmonary TB – lymph nodes, pleura, genitourinary tract, bones and joint meninges, peritoneum, pericardium and head and neck region. Head n neck TB involves larynx, middle ear nasal cavity, nasopharynx, oral cavity, parotid gland, esophagus and spine.²

ORAL MANIFESTATION
Chronic painless ulcer mainly on lateral borders of tongue. Lesion may present as nodular, granular or rarely firm leukoplakic areas. Secondary oral lesions – tongue, palate and lip Primary oral tuberculosis without pulmonary involvement is rare. usually involves gingiva, mucobuccal fold and areas of inflammation adjacent to teeth or in extraction sites. Primary oral lesions – enlarged lymph nodes Tuberculous osteomyelitis – reported in jaws and appears as ill defined areas of radiolucency.
DIAGNOSIS

TREATMENT

<table>
<thead>
<tr>
<th>TB category</th>
<th>Initial phase</th>
<th>Continuation phase</th>
<th>Total duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2HRZE (S)</td>
<td>4HR 6HE</td>
<td>6 8</td>
</tr>
<tr>
<td>2</td>
<td>2HRZES + 1 HRZE</td>
<td>5 HRE</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>2HRZ</td>
<td>4 HR 6HE</td>
<td>6 8</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Leprosy
Also known as hansens disease. Chronic granulomatous disease- skin and peripheral nerves.
Mycobacterium leprae is the causative organism. Impairment of nerve function – major disabilities. WHO 7,20,000 new cases reported every year. Endemic in developing countries as India Myanmar etc. Growth occurs – cooler body sites – skin mucosa, peripheral nerves.
Incubation period 3-5 yrs. Tuberculous and lepromatous two clinical pattern.3

Clinical Features
Males more affected. Age of diagnosis 10-20 yrs.
Skin peripheral nerves eyes and bones affected.

Oral Manifestations
Oral lesions frequently seen in lepromatous form as papules,plaques,nodules,non specific erosion and ulceration involving tongue, buccal mucosa and palate. Changes affecting facial bones – faciesleprosa. Atrophy of anterior nasal spine, and recession of maxillary alveolar process and endonasal inflammatory changes. Alveolar destruction limited – max ant region – loosening/loss of teeth. Inflammation of nasal cavity – palatal perforation and oronasal communication. Dental pulp may be affected leading to pulpal necrosis. Microorganisms accumulate within mylenated nerves in pulp – resulting in vascular damage which causes reddish discoloration of tooth.

Investigation
Cardinal features
1. skin lesions esptuberculoid2. thickened peripheral nerve3. acid fast bacilli on skin smear or biopsy
Management.

Principle of leprosy treatment
Stop the infection with chemotherapy. Treat reactions. Educate the patient about leprosy. Prevent disability. Support the patient socially and psychologically.

Syphilis
Also known as LEUS – chronic sexually transmitted disease. Caused by Treponemapallidum.Diverse clinical
presentation characterized by periods of active disease and latency. *T. pallidum* rapidly penetrates intact mucosa or microscopic abrasions in the skin. Enters blood and lymphatics to produce systemic infection. Survives in untreated patients for years. Transmitted from syphilitic women to fetus.

**Clinical Features**

**Three stages**

Primary, secondary, tertiary. Primary stage: chancre – site of inoculation – 21 days post infection. Chancre is painless papule which later becomes ulcerated. Primary lesion on genitalia with regional lymphadenopathy. Primary lesion resolves – 4-6 week with or without treatment. Painless ulcers occurs at site where it is not visible. Hematogenous dissemination of pathogens in primary stage results in manifestation of secondary syphilis bout 6-8 weeks later. Common manifestations maculopapular rash affecting flank, shoulder, arm, chest, hand, soles and feet. Generalized non tender lymphadenopathy. Less common features of secondary syphilis mucous patches, condylomata lata, alopecia, meningitis, myalgia, ocular complaints, hepatic, pulmonary and neurologic involvement. Secondary lesions resolve with or without treatment - infection enters latent stage. Tertiary syphilis characterized by cardiovascular disease, neurosyphilis or gumma. Commonly involved sites are skin and skeletal system, mouth, upper respiratory tract, larynx, liver and stomach. Early congenital syphilis includes rhinitis, mucocutaneous lesion, periostitis, hepatosplenomegaly, lymphadenopathy, anaemia, jaundice, leukocytosis and thrombocytopenia. Hutchinson triad: interstitial keratitis of cornea, sensorinural hearing loss, and dental abnormalities.

**Oral Manifestation**

Oral manifestation is rare. Primary syphilis – solitary ulcers with indurated margins on lip, tongue and palate. Ulcer deep – accompanied by cervical lymphadenopathy. Chancre heals within 7-10 days.

Secondary syphilis maculopapular rash and nodular mucosal lesions. Mucosal patches seen on lips, oral mucosa, tongue, palate and pharynx. Mucous patches – painless, oval to crescentic erosions surrounded by red periphery. Serpigenous lesions arise de novo or form by coalescence of number of mucous patches. Condylomata verrucous plaques seen in secondary syphilis.


**Diagnosis and Investigation**

Diagnosis based on clinical signs and symptoms. Cannot be detected by culture. Two types of serologic tests 1. Treponemal 2. Non treponemal

Non treponemal tests are rapid plasma reagin (RPR) and Venereal Disease Research Laboratory (VDRL). Non treponemal tests measures IgG and IgM directed against cardiolipin cholesterol antigen complex – used for screening or quantification of serum antibody.

Treponemal tests – confirmation of reactive non treponemal results and includes fluocentreponemal antibody – absorbed test (FTA – ABS) and T Pallidum particle agglutination assay(TPPA)

**Management**


**Fungal Infections**

**Blastomycosis**

Caused by Blastomyces dermatitidis - dimorphic fungus – grows in soil and decaying wood. Inhalation of conidia. In lungs at body temp conidia are transformed into yeasts that multiply through budding. Infection in lungs – asymptomatic or develop mild non specific flu like symptoms. Hematogenous spread may occur 3 clinical forms

a) Pulmonary blastomycosis
b) Disseminated blastomycosis
c) Cutaneous blastomycosis

Pulmonary can be Acute or Chronic. Acute presents with productive cough, chest pain, dyspnoea, fever, night sweats. Chronic at times mistaken for TB.

Oral involvement is rare or can be present as ulcers or exophytic mucosal lesions.
Diagnosis usually made on identification of blastomycosisdermatitidis in a tissue biopsy or cytological smear of infected body fluid. Organism appear as round yeast cell which divides by broad based budding. Diagnosis confirmed by culture. Treatment based on severity of disease. Mild to moderate Itraconazole 6 – 12 months. Severe meningeal lesions and immunocompromised patients with Amphotericin B for 10 weeks.

Histoplasmosis

Mucormycosis
Also known as Phycomycosis or Zygomycosis. Infection with saprophytic fungus – occurs in soil. Can be cultured regularly from human nose, throat and oral cavity. Occurs in individuals with decreased host response. Fungus invades arteries and causes damage secondary to thrombosis and ischaemia. Symptoms ptosis, fever, swelling of cheek, and paresthesia of face.

Oral Manifestation
Ulceration of palate. Lesion large and deep – denudation of underlying bone. Ulcers also reported on lips, gingiva and alveolar ridge. Biopsy performed to confirm diagnosis. Specimen shows necrosis and non septate hyphae by Periodic acid Schiff stain

Treatment
Early cases – combination of surgical debridement and systemic administration of Amphotericin B 50-100 mg QID for 3 months. Proper management of underlying disorders

Aspergillosis
Fungal infection – Aspergillus species. Inhaled organisms can cause allergic fungal sinusitis, allergic pulmonary aspergillosis or asthma. Aspergillus fumigates and aspergillusflavus – commonly cause human aspergillosis. Diagnosis based on clinical features, culture and histopathology, Multiple septate hyphae seen.

Treatment
Amphotericin B and Itraconazole. At times surgical debridement

Foreign Body Granulomas
Exogenous : silica,beryllium, glass, talc
Endogenous: hair, keratin, amyloid
Clinically varies from localized to superficial erosion and ulceration. In oral cavity gingiva is the most common site. Clinically localized change in gingival color, ulceration or diffuse erythma. Lesion begins at interdental papilla. Important diagnostic clue is – condition does not resolve with improvement of oral hygiene. Biopsy shows granulomas and foreign body giant cells in absence of microorganisms. Identified by H $ E stain.

Management
Excision of offending agent and excision of involved tissue

Wegeners Granulomatosis
Systemic autoimmune granulomatous disease. Presents with classical triad of:
1. Necrotizing granulomatous inflammation involving upper respiratory tract
2. Necrotizing glomerulonephritis
3. Systemic vasculitis involving small to medium sized vessels.

Clinical Features
Affects mainly upper and lower respiratory tract. Renal disease develops rapidly. Some cases restricted to skin known as wegners granulomatosis. Pulmonary involvement shows cough, hemoptysis, dyspnoea and chest discomfort. In asymptomatic patients abnormal chest radiograph. Early glomerulonephritis presents with proteinuria, hematuria and red blood cell casts in urine. Progression leads to renal failure when no t/t done. Active disease characterized by malaise, fever, night sweats
lymphadenopathy, arthralgia
erythema nodosum, bilateral hilar

**Form**
Lofgren Syndrome
Heerfordt Syndrome

**Lofgren Syndrome**
Form of acute sarcoidosis – white females – erythema nodosum, bilateral hilar lymphadenopathy, arthralgia

**Heerfordt syndrome**
parotid enlargement, anterior uveitis, facial paralysis and fever

**Oral Manifestation**
Rare except salivary gland and lymph node involvement. Site: buccal mucosa, gingiva, lips, floor of the mouth, tongue and palate. Lesions present as submucoosal masses - colour from normal to brownish red –hyperkeratotic. Involvement of major and minor salivary glands may lead to xerostomia. Bilateral involvement of major salivary glands. Intraosseous lesions less common. If present appears as non expansilell defined radiolucent areas accompanied by tooth mobility due to alveolar bone loss

**Diagnosis**

**Management**
Diagnosis followed by 3-12 months period of observation. Immediate t/t indicated for neurological, cardiac, severe ocular, advanced pulmonary and disfiguring cutaneous disease. Systemic corticosteroids. Pts with periodontal disease and candidiasis necessitating measures. Systemic corticosteroid therapy result in adrenal suppression requires special precautions before oral surgical intervention.

**Orofacial Granulomatosis**
Clinical and pathologic term - group of conditions affecting oral and maxillofacial regions and characterized microscopically by non caseating granulomatous inflammation. Etiology unknown – produce abnormal immune reaction. Cytokine production by monoclonal lymphocytic proliferation can stimulate granuloma formation. 

**Clinical Features**
Painless, persistent diffuse swelling involving one or both lips (macrochelia). Unilateral swelling involving whole lips. Early phase swelling soft intermittent and recurrent. Later permanent and fibrotic. Generalized edema, erythema and nonspecific erosions or
ulcerations seen in mouth. Gingival swelling in some cases. Swelling at other places of the face with or without lip involvement. Other manifestations fissures of tongue, taste alteration, decreased salivary production and cobble stone appearance of bucal mucosa. Swelling limited to lips – Cheilitis Granulomatosa - Swelling associated with fissured tongue and h/o recurrent facial paralysis – Melkerson Rosenthal syndrome.45

Diagnosis
PAS stain Grocottmethamine silver stain, ZiehlNeelsen stain and Gram stain applied to the lesion donot show fungal or specific bacterial organisms. Systemic workup as clinical, laboratory and radiographic investigation to rule out underlying local or systemic disease. Oral foci of infection identified and treated. Chest radiograph and serum levels of ACE obtained to screen for evidence of sarcoidosis. Complete blood count, ESR and serum levels of folic acid, vit b12and iron useful in pts with unusual gastrointestinal manifestation. Specialized gastrointestinal examination to assess for Crohn's disease. Tuberculin test and chest radiograph to rule out tuberculosis.

Management
Intralesional corticosteroids. Response fast but relapse common. Systemic corticosteroids – long term. Other measures hydroxychloroquines, methotrexate, clofazimine, metronidazole, or minocycline alone or in combination with oral prednisolone, thalidomide, dapsone.

Crohn's Disease
Chronic relapsing immunologically mediated inflammatory bowel disorder. Etiology and pathogenesis not clearly defined. Inappropriate acquired T cell immune response to commensal enteric bacteria developing in genetically susceptible host T cells implicated in Crohn's disease are primarily activated CD4 + Th 1 lymphocytes which secrete cytokins such as IL 12, TNF.

Clinical Features
Prevalent in western countries. High economic status and active smoking increases risk of disease. Peak age of onset 15 – 30 yrs. Affects any part of gastrointestinal tract with terminal ileum being most common. Symptoms are long standing diarrhoea, abdominal pain and weight loss. Malaise, anorexia and fever also seen in some pts. Transmural inflammation of gut results in fissures, abscess, fistula, thickening of bowel wall and limited distensibility. Aphths like superficial ulceration – cobble stone appearance of bowel mucosa. Extraintestinal manifestations seen and includes dermatologic conditions as erythema nodosum, pyodermagangrenosum, pyodermatitisvegetans, and neutrophilicdermatoses. Ocular complications include conjunctivitis, anterior uveitis and episcleritis.

Oral Manifestation
Occurs at any time during the course of the disease. Diffuse or nodular swelling of oral and perioral tissues, a cobblestone appearance of oral mucosa and deep linear ulcers involving vestibule. Aphthous ulcers can also be seen. Fibro epithelial hyperplasia, granulomatous gingivitis, angular cheilitis, persistent submandibular and superficial cervical lymphadenopathy and metallic dysgusia.

Diagnosis
Confirmed by clinical evaluation and a combination of endoscopic, histopathological, radiographic and biochemical investigation.

Management
Anti-inflammatory and immunosuppressive medications such sulfasalazin, prednisone, Azathioprine and 6-Mercaptopurine. Anti TNF antibody known as infliximab – effective as it blocks TNF – key inflammatory cytokine and mediator of intestinal inflammation. Surgery required for 50 -80% of patients – related to duration of disease and site of involvement. Pts shows a variable response to topical and systemic corticosteroid therapy

CONCLUSION
We as oral physicians should be able to diagnose all the granulomatous disease properly for a good treatment.

REFERENCES

5. Orofacial Granulomatous inflammation. a detailed review. Trough Pubmed.