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Granulomatous Lesions in Head and Neck Region: A Review

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Abstract: *Granulomatous diseases have plagued humans for million years, with evidence of tuberculosis infection in Egyptians mummies and description of syphilis has also been said to have been described by Hippocrates and was recognized as a veneral disease in the fifteenth century. The advent of modern pathology with improved microscopic staining techniques & communication between researches spawned this new category of granulomatous diseases in early twentieth century. Recognition of the granulomatous pattern in a biopsy specimen is important because of the limited number of possible conditions that cause it and the significance of the diagnosis associated with lesion i.e. for specific treatment and outcome of the disease.*

Keywords: *Grauloma, Granulomatous leions, Necrosis, Giant cells, epithelioid macrophages.*

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I. Introduction

The term Granulomatous diseases include those conditions characterized by histological presence of Granuloma resembling those of tuberculosis as well as conditions without microscopic granuloma formation but with prominent proliferation of Granulation tissue[2].The term "**Granuloma"** is coined by **"Virchow"** in the year 1864. The word granuloma meaning circumscribed granule like lesion, and oma (suffix used for true tumours). Granuloma is a focus of chronic inflammation consisting of a microscopic aggregation of macrophages that are transformed into epithelial – like cells, surrounded by a collar of mononuclear leukocytes, principally lymphocytes and occasionally plasma cells.

Robert Koch developed a method of staining and was able to differentiate infectious and noninfectious Granulomatous diseases[1].

Depending on the defense capacity of the host and duration of response, inflammation can be classified as acute and chronic.

Acute inflammation is of short duration and represents the early body reaction and is usually followed by repair. Here the polymorphonuclear neutrophils are the predominant inflammatory cells.

Chronic inflammation is of longer duration and occurs either often the causative agent of acute inflammation persists for a long time or, the stimulus is such that it induces chronic inflammation from the beginning. Here the lymphocytes, plasma cells and macrophages are the predominant inflammatory cells.

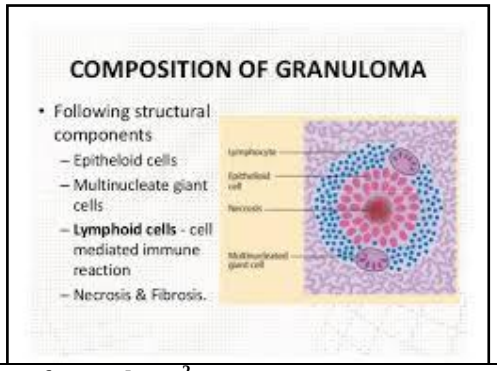
Granulomatous inflammation is a distinctive pattern of chronic inflammation that is encountered in a limited number of infectious and some non infectious conditions. It is a protective response to chronic infection or foreign material, preventing dissemination and restricting inflammation[2].

Granulomatous inflammation of the oral soft &hard tissues is an uncommon occurrence but when found it presents a definite diagnostic dilemma because of the wide variety of possible etiologic diseases & rather generic appearance of the individual lesions[1]. Granuloma is a focus of chronic inflammation consisting of a microscopic aggregation of macrophages that are transformed into epithelial – like cells, surrounded by a collar of mononuclear leukocytes, principally lymphocytes and occasionally plasma cells.Granulomas are of two types foreign body granulomas and immune mediated granulomas. The nuclei in the giant cells may be arranged haphazardly(foreign body) or peripherally often in the shape of a horse shoe(langhans type).There is no functional difference between two types of giant cells[1]. The epithelioid shaped macrophages represent activated cells that on coalescing produces multinucleated giant cells.Beside the presence of epithelioid cells, giant cells, and lymphoid cells, granulomas may have necrosis and fibrosis. Epithelioid cells, so called

because of their epithelial cell like appearance ,are modified macrophages/histiocytes which are somewhat elongated, having pale staining abundant cytoplasm ,vesicular and lightly stained slipper shaped nucleus.

An important feature of granulomas is presence or absence of necrosis. Necrosis refers to dead cells , under the microscope, appear as a mass of formless debris with **no nuclei present**.. The identification of necrosis in granulomas is important because granulomas with necrosis tends to have infectious cause[2].

FIGURE I



II. Pathophysiology of granuloma[2]

INJURY

↓

FAILURE TO DIGEST AGENT

↓

WEAK ACUTE INFLAMMATORY RESPONSE

↓

PERSISTANCE OF INJURIOUS AGENT

↙ ↘

T-CELL MEDIATED IMMUNE RESPONSE POORLY DIGESTABLE AGENT

↓

ACTIVATION OF CD4+T CELLS(Release of lymphokines IL-1,IL-2,growth factors,interferon α and ϒ)

MONOCYTE CHEMOTACTIC FACTOR

↓

ACCUMULATION OF TISSUE MACROPHAGES

↓

MACROPHAGES ACTIVATED BY INTERFERONϒ

↓

TRANSFORMED INTO EPITHELIOID CELLS AND GIANT CELLS.

↓

FORMATION OF GRANULOMA

II. Classification of granulomatous lesions in head and neck region:

Based on etiology[1]:

1.INFECTIONS –

BACTERIAL	FUNGAL	SPIROCHETAL	PARASITIC
Tuberculosis	Histoplasmosis	Syphilis	Leishmaniasis
Leprosy	Blastomycosis		Myiasis
Non tuberculous mycobacterial infections.	Phycomycosis (mucormycosis)		Toxoplasmosis

Actinomycosis	Aspergillosis		
Klebsiella rhinoscleromatis	Candidiasis		
Anthrax	Cryptococcus		
Brucellosis	Rhinosporidiasis		

2.TRAUMATIC ETIOLOGY:
i)Pyogenic granuloma
ii) Reparative granuloma
3.FOREIGN BODY ETIOLOGY:
i) Oral foreign body reactions(suture,hair,amalgam,endodontic sealer etc)
ii) Cholesterol granuloma
iii) Cocaine induced midline granuloma
4.NEOPLASTIC
i)Histiocytosis X-
a)Eoisinophilic granuloma.
b)Hand schuller Christian disease
c) LettererSiwe disease.
ii)Benign fibrous histiocytoma

5. Auto immune & vascular disease
i) Wegener's granulomatosis
ii) Systemic lupus erythematosis
iii) Sjogren's syndrome
6) Developmental
Melkerson Rosenthal syndrome
7) Congenital chronic granulomatous disease of childhood.
8) Unknown etiology
i)Sarcoidosis
ii)Crohn's disease

CLASSIFICATION BASED ON ORAL GRANULOMAS[3]

Classification	**Type of infectious agent**
1. Nonspecific granulomas	Periapical granuloma
	Pyogenic granuloma
	Traumatic granuloma
2.Foreign body granuloma	Particulate materials(dental cements, Abrasives)
3.Specific granulomas	
Caseating granulomas	Mycobacterium tuberculosis
	Tularemia
	Cat-scratch fever
Noncaseating granuloma	Mycobacterium avium intracellulare
	Histoplasmosis
	Blastomycosis
	Coccidiomycosis
	Cryptococcosis
4. Orofacial granulomatosis	Chelitis granulomatosis
	Melkersson Rosenthal syndrome
	Heerfordt syndrome
	Crohn disease and Sarcoidosis

III. Infectious Granulomatous Inflammation

Mycobacterium tuberculosis:

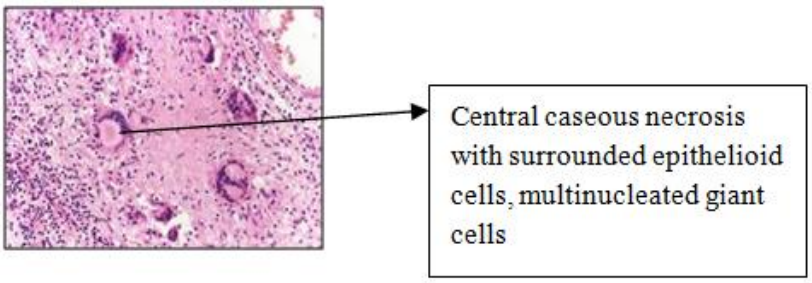
Tuberculosis is the second leading infectious cause of death in the world after HIV, affecting 1.7 billion people worldwide and killing 1.7 million each year.

Most cases tuberculosis are pulmonary and acquired by person to person transmission of air borne droplets of organisms. Oropharyngeal and intestinal tuberculosis are acquired by drinking dairy milk contaminated with Mycobacterium bovis.(strain of tuberculosis).

Infection with M.tuberculosis is different from disease. Infection which is the presence of the organism may or may not cause clinically significant disease. Viable organisms may remain dormant for decades until immunity is suppressed, infection may then be reactivated to produce disease[4]

Histopathology: primary tuberculosis infect the lungs.as sensitization develops a 1 to 1.5cm,area of gray white inflammation known as **ghon's focus** develops in the lung. in most cases center of the **ghon' s focus** undergo caseous necrosis.

FIGURE II.



ACTINOMYCOSIS:

Actinomycosis is a sub acute to chronic bacterial infection characterized by contiguous spread, suppurative granulomatous inflammation leads to formation of multiple abscesses and sinus tracts that may discharge **sulphur granules**[5]The causative organisms are non motile, non spore forming, non acid fast, gram positive pleomorphic, anaerobic to microaerophilic filamentous bacterial rods. The most common actinomyces species are **Actinomyces Israeli, Actinomyces naesulindi**

Actinomycosis in human beings occur in four main clinical forms:

1) Cervicofacial actinomycosis(moct common)
2) Thoracic actinomycosis
3) Abdominal actinomycosis
4) Pelvic actinomycosis.

HISTOLOGICAL FEATURES:

The typical lesion of actinomycosis, either in soft tissues or in bone, is essentially a granulomatous showing central abscess formation within which may be seen the characteristic colonies of microorganisms. These colonies appear to be floating in a sea of polymorph nuclear leukocytes, often associated with multinucleated giant cells and macrophages around the periphery of the lesion. The individual colony, which may appear round or lobulated, is made up of meshwork of filaments that stain with hematoxylin, but shows eosinophilia of the peripheral club shaped ends of the filaments. This peculiar appearance of the colonies, with peripheral radiating filaments, is the basis often termed as **ray fungus**.

SYPHILIS:

Caused by Treponema pallidum, a spirochete. It is a gram positive, motile, microaerophilic spirochete best demonstrated by the dark field microscope, since it stains poorly except by silver impregnation and immunofluorescence techniques. And it cannot be grown in cultures. Treponema(trepos, meaning to turn, and nema, meaning thread)

Syphilis is a chronic veneral disease with multiple clinical presentations . the organism can easily invade any mucous membrane and cause lymphadenopathy . The clinical presentation can involve chancre formation, regional lymphadenopathy, widespread mucocutaneous lesions, condyloma lata, cardiovascular syphilis, nerosyphilis, and syphilictic gumma, according to the natural course of the disease[6]. Even transplacental transmission occurs readily, and active disease during pregnancy results in congenital defects.

Syphilis can be classified as either acquired or congenital.

Histopathology: Microscopically chancre contains an intense infiltrate of plasma cells, with scattered macrophages and lymphocytes. The microorganisms present in the tissue can be demonstrated by silver stain. The regional nodes are enlarged due to non specific acute or chronic lymphadenitis, plasma cell rich infiltrate or granulomas.

Histoplasmosis:

Histoplasmosis is caused by the fungus **Histoplasma capsulatum** that grows as a mold in soil and as a yeast in human and animal hosts. The organism growing in soil produces **spore forms (conidia**). Breathing the airborne conidia causes infection[7.]Oral and pharyngeal manifestations can occur as an isolated symptom or as a part of disseminated process associated with immunosuppression especially with HIV and diabetes

Histologic features: Histoplasmosis appears basically to be a granulomatous infection which affects chiefly the reticuloendothelial system. Thus the organisms are found in large number of phagocytic cells and appear as a tiny intracellular structures measuring more than 1µm in diameter. Lesional tissue shows either a diffuse infiltrate of macrophages or, collection of macrophages organized in to granuloma.

IV. Traumatic Etiology

Pyogenic granuloma is a common tumour like growth of the oral cavity that has been considered as non neoplastic in nature. The pypgenic granuloma is thought to represent an excuberant tissue response to local irritation or trauma. Is a smooth or lobulated mass that is usually **pedunculated**? The surface is characteristically ulcerated and ranges from pink to red to purple, depending on the age of the lesion[8].

Histopathologic features: shows highly vascular proliferation that resembles granulation tissue. Numerous small and large endothelial cells that are engorged with red blood cells. The surface is usually ulcerated and replaced with fibroplurulent membrane. A mixed inflammatory cell infiltrate of neutrophils, plasma cells and lymphocytes is evident. Older lesions may have areas with a more fibrous appearance[8,9].

V. Oral Foreign Body Granuloma

Oral foreign body granuloma formation has been linked to a variety of conditions.like, silica granuloma of the lip due to the injection of silicone for lip enhancement[10], **foreign-body giant cell reaction** elicited by an haemostatic alginate, and accidental implantation of dental amalgam and by injecting cosmetic dermal fillers like calcium hydroxyapatite and poly lactic acid can cause **foreign body granulomas**. Oral Pulse granuloma is the term used to describe oral inflammatory lesions characterized microscopically by the presence of inflammatory gaint cells and hyaline rings. It is a rare entity, representing a foreign body reaction to vegetable particles[11]

Cocaine induced mid line granuloma:

The most common sign of habitual cocaine use recognized by dermatologists is nasal septal perforation and less common is the far more mid facial necrosis reported almost exclusively in the mid facial region. Even large ulcerations can be seen on the upper lip, nose and para nasal sinuses induced by chronic nasal insufflations of cocaine[12]

Histopathology: on examination it mimics wegeners granulomatosa. It appears as a pattern of mixed inflammation centered around blood vessels. The connective tissue adjacent to the vessel has an inflammatory cellular infiltrate, which contains a variable mixture of histiocytes, lymphocytes, eoisinophils, and multinucleated giant cells.

VI. Neoplastic

Histiocytosis x- the term histiocytosis is an "umbrella" designation for a variety of proliferative disorders of dendritic cells or macrophages. some, such as rare histiocytic lymphomas are clearly malignant, whereas others, such as reactive proliferations of macrophages in lymph nodes are clearly benign. Lying between these two extremes are langerhans cell histiocytosis[2].

Langerhans cell histiocytosis presents as several clinicopathological entities i.e

- Multifocal multisystem langerhans cell histiocytosis(letterer siwe disease)
- Unifocal and multifocal unisystem langerhans cell histiocytosis(eosinophilic granuloma)
- Hand schuller Christian disease[8]

Histopathologic features: The bone lesions of patients with langerhan's cell histiocytosis show a diffuse infiltration of large, pale staining mononuclear cells that resembles histiocytes. These cells have indistinct cytoplasmic borders and rounded or indented vesicular nuclei. Plasma cells, lymphocytes and multinucleated giant cells are often seen and areas of necrosis and hemorrhage may be present.

VII. Unknown Etiology

Sarcoidosis: is a multisystem granulomatous disorder of unknown cause. **Jonathan Hutchinson** initially described the disease in 1875, but **Boeck** coined the term Sarcoidosis. The evidence implicates improper degradation of antigenic material with the formation of non caseating granulomatous inflammation, but the nature of the antigen is unknown[10].

Histopathologic features: microscopic examination of sarcoidosis exhibit a classic picture of granulomatous inflammation. Characterized by circumscribed collection of histiocytes,lymphocytes and multinucleated giant

cells. The granulomas often contain **basophilic calcifications,** known as schaumann bodies or stellate inclusions, known as **asteroid bodies.**[13]

VIII. Autoimmune And Vascular Diseases

Wegeners granulomatosis: Is a well recognized, although uncommon, disease process of unknown cause. Basically involves vascular, renal, and respiratory system, causing necrotizing granulomatous lesions of the respiratory tract, necrotizing glomerulonephritis, and systemic vasculitis of small arteries and veins. It is also known as "**Granulomatosis with polyangitis**[14]: involvement of gingival has been the most common and characteristic manifestation, and is termed as **strawberry gingivitis**

Histopathologic features: Oral biopsy specimen shows pseudoepitheliomatous hyperplasia and subepithelial abscesses. The gingival and other lesions show a nonspecific granulomatous pattern with scattered giant cells[8].

IX. Orofacial Granulomatosis

It has become a well accepted and unifying term encompassing a variety of clinical presentation that on biopsy, reveals the presence of nonspecific granulomatous inflammation. The clinical presentation of orofacial granulomatosis is highly variable. The most frequent site of involvement is the lips i.e. the non tender, persistent swelling that may involve one or both lips which is termed as chelitis granulomatosa, if it is associated with facial paralysis and a fissured tongue rather it is termed as melkerson Rosenthal syndrome[16].

Histopathologic features: Biopsy of chelitis granulomatosa may reveal edema in the superficial lamina propria with dilation of lymphatic vessels and scattered lymphocytes seen diffusely and in clusters. Fibrosis may be present in long term lesions. Scattered aggregates of non caseating granulomatous inflammation, consisting of lymphocytes and epitheliod histiocytes are present with or without giant cells.

X. Conclusion

The term granulomatous diseases include those conditions characterized by histologic appearance of granuloma resembling those of tuberculosis as well as condition without microscopic granuloma formation but with prominent proliferation of granulation tissue. Granulomatous diseases of the oral soft and hard tissues are an uncommon occurrence but when found it presents as a definite diagnostic dilemma because of the wide variety of possible etiologic factors. A wide variety of immunologic, idiopathic, neoplastic, infectious, and fungal processes can cause a chronic granulomatous reaction in the head and the neck. A granuloma is a focal area of chronic inflammation produced by circulating monocytes as part of an immunologic process. A granulomatous reaction is characterized histologically transformed macrophages (epithelioid cells) surrounded by lymphocytes. These epithelioid cells may later fuse to form giant cells. The most common differential diagnosis include foreign body reactions, infections, crohn's disease, sarcoidosis, orofacial granulomatosis because of the relatively nonspecific clinical findings associated with theses granulomatous disease, the microscopic diagnosis of granulomatous inflammation often present a diagnostic dialemma for the clinician. Management of the granulomatous lesions is started after the discovery of the etiologic factor.

Thus often an extensive clinical, microscopic and laboratory evaluation is needed to identify the source of granulomatous lesions.

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