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The Granulomatous Lesions of Oral Tissue - A Brief Review

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ABSTRACT

Granulomatous inflammation represents a unique form of the chronic inflammatory response. Their occurrence in oral soft & hard tissues is an uncommon but represents a diagnostic dilemma because of the wide variety of possible etiologic factors. Recognition is important because of the limited number of possible conditions that causes it and for specific treatment and outcome of the disease. They often have systemic manifestations that affect organs throughout the body and share similar histogenesis. Therefore, an extensive clinical, microscopic and laboratory evaluation is required to identify the source of the oral granulomatous diseases.

Key words: Granulomatous inflammation, Granuloma, Oral granulomatous lesion

INTRODUCTION

The term granulomatous inflammation is a unique form of chronic stage of inflammation in which the presence of true distinct structure called Granuloma, composed of epithelioid-shaped macrophages, multinucleated giant cells, lymphocytes and fibroblasts. The term is coined by "Virchow" in the year 1864. [1,2] The clinical findings associated with granulomatous inflammation are usually variable and often indistinct; has a multifactorial etiology and may arise as a reaction to environmental or genetic factors, infectious organisms, or idiopathic [1 2]

Definition

A *granuloma* is an aggregate of epithelioid cells that also contain other type of cells such as lymphocytes and giant cells. Granulomatous inflammation is characterized by the collections of activated macrophages, often with T lymphocytes, and sometimes associated with central necrosis. The diseases comprise some of the most widespread and serious in the world, such as tuberculosis and leprosy.[3 4]

Structure and formation of a Granuloma

A granuloma is a distinct structure composed of epithelioid-shaped macrophages surrounded by a rim of lymphocytes. Fibroblasts and collagen fibers were also seen surrounding the lymphocytes. The epithelioid cells represent an activated state that upon coalescing, produces multinucleated giant cells.[2] The nuclei may be arranged either haphazardly (foreign body-type) or peripherally (in the shape of a horseshoe _ Langhan-type). In some instances, granuloma may also exhibit a central area of caseous necrosis.[2]

The formation of a granuloma is a cellular attempt in response towards an offending agent which is often difficult to eradicate. In this reaction there is a strong activation of T lymphocytes, leading to macrophage activation, causing an injury to normal tissues. The activated macrophages may develop abundant cytoplasm and begin to

resemble epithelial cells, called as epithelioid cells. Some activated macrophages may fuse together forming the multinucleated giant cells.[4]

Etiology:

The most common causes of granulomatous inflammation involving the oral tissues include foreign body reactions, infections, Crohn's disease, sarcoidosis, and orofacial granulomatosis.[3]

Types of Granulomas

There are two types of granulomas, which differ in their pathogenesis viz foreign body granuloma and immune mediated granuloma.[2]

Foreign body granuloma: Incited by relatively inert foreign bodies, in the absence of T cell–mediated immune responses. They are formed around foreign materials that are large enough to preclude phagocytosis by a macrophage and do not incite any specific inflammatory or immune response. Epithelioid cells and giant cells are opposed to the surface of the foreign body. The foreign material can usually be identified in the center of the granuloma, if viewed with polarized light which appears refractile. [2 4]

Immune mediated granuloma: Caused by a variety of agents that are capable of inducing a persistent T cell–mediated immune response. Produces granuloma when the inciting agent is difficult to eradicate, such as a persistent microbe or a self-antigen. The macrophage activates T cells to produce cytokines, such as IL2 and IL4 which further activates other T cells and IFNγ. These activated cytokines or IFNγ may transform the cells into epithelioid cells and multinucleate giant cells. [2 4]

Granulomatous Inflammation due to Infections (specific type)

Bacterial Infection

Syphilis

Caused by Treponema pallidum, a spirochete best demonstrated by the dark field microscope. It cannot be grown in culture and a chronic venereal disease with multiple clinical presentations. The organism can easily invade any mucous membrane and causes lymphadenopathy. The clinical presentations involve chancre formation, regional lymphadenopathy, widespread mucocutaneous lesions, condyloma lata, cardiovascular syphilis, neurosyphilis, and syphilitic gumma, according to the natural course of the disease. Even transplacental transmission occurs during pregnancy results in congenital defects.[5 6 7 9]

Microscopically chancre contains an intense infiltrate of plasma cells, with scattered macrophages and lymphocytes. The microorganisms can be demonstrated by silver stain. The regional nodes are enlarged due to non-specific acute or chronic lymphadenitis, and plasma cell rich infiltrate. [5 7 9]

Tuberculosis

Tuberculosis is the second leading infectious disease in the world that causes death after HIV. Most cases are pulmonary and acquired by person-to-person transmission from air borne droplets which constitute the organisms. [5 6 7 8 9]Oropharyngeal and intestinal tuberculosis are acquired by drinking contaminated dairy milk with Mycobacterium bovis (strain of tuberculosis). The disease rapidly declined in developed countries due to improved nutrition and hygiene, BCG immunization and chemotherapy but remain prevalent in developing countries. Patients with immunosuppression are particular risk. Other risk groups are elderly and alcoholics. [5 7 8 9]

Histopathology shows the infected lungs develop a 1 to 1.5cm area of gray white inflammation known as Ghon's focus. In most cases, center of the Ghon's focus undergo caseous necrosis.

Leprosy

A chronic infectious disease produced by *Mycobacterium leprae*. There are two main clinical presentations that are related to immune reaction towards the organism. The first, called *Tuberculoid leprosy,* develops in patients with a high immune reaction. *Lepromatous leprosy,* is seen in patients who demonstrate a reduced cell-mediated immune response. [5 7 8 9]

Biopsy specimens of paucibacillary leprosy typically reveals the tuberculoid pattern that demonstrates granulomatous inflammation with well-formed clusters of epithelioid histiocytes, lymphocytes, and multinucleated giant cells. Demonstrated with the use of acid-fast stains. [5 7 8 9]

Actinomycosis

Actinomycosis is a sub-acute to chronic bacterial infection characterized by, suppurative granulomatous inflammation leads to formation of multiple abscesses and sinus tracts may discharge sulphur granules. The causative organisms are filamentous, branching, gram-positive anaerobic bacteria. The most common species are Actinomyces Israeli (majority), A.viscosus being closely second. Less frequently are A. naeslundii, A. meyeri, A. pyogenes, A. viscosus, and A. bovis, [5 7 8 9]

Typical lesion either in soft tissues or in bone, shows granulomatous inflammation with central abscess formation within which the characteristic colonies of microorganisms are visible. These colonies appear to floating in a sea of polymorphonuclear leukocytes, often associated with multinucleated giant cells and macrophages. Individual colony may appear as round or lobulated, made up of meshwork of filaments that stains with hematoxylin, but shows eosinophilia of peripheral club shaped ends of the filaments. This peculiar appearance of the colonies, with peripheral radiating filaments often termed as ray fungus. [5 7 8 9]

Fungal Infection:

Blastomycosis

Blastomycosis is a relatively uncommon disease caused by the dimorphic fungus known as Blastomyces dermatitidis. The organism is rarely isolated from its natural habitat. It seems to prefer rich, moist soil where it grows as a mold. Much of the region in which it grows overlaps the territory associated with *H. capsulatum* [5 7 10]

The histopathological examination reveals a mixture of acute inflammation and granulomatous inflammation surrounding variable numbers of yeasts. These organisms are 8 to 20 μm in diameter, characterized by double refractile cell wall and an attachment between the budding daughter cell and the parent cell. The organisms can be detected more easily using special stains, such as the gomori methenamine silver (GMS) and PAS methods. [5 7 10]

Coccidioidomycosis

Coccidioides immitis is the fungal organism responsible for coccidioidomycosis. It grows saprophytically in the alkaline, and desert soil. They are dimorphic organism appears as a mold in its natural environment of soil or as a yeast in tissues of the infected host. Arthrospores produced by the mold become airborne and can be inhaled into the lungs by the human host, producing infection. [5 7 10]

Biopsy material shows large (20 to 60 μm), round spherules that may contain numerous endospores. The host response may be variable, ranging from a suppurative, neutrophilic infiltrate to a granulomatous inflammatory response. In some case the two patterns of inflammation are seen concurrently. Special stains, such as the PAS and Grocott-Gomori methenamine silver methods, enable the pathologist to identify the organism more readily. [5 7 10]

Cryptococcosis

Cryptococcosis also primarily affects the lungs of immunosuppressed individuals. The causative agent is *Cryptococcus*

neoformans; a yeast found in bird droppings. Face, neck, and scalp are common sites of cutaneous lesions. Oral lesions are extremely rare but do occur. When present, the oral lesions show superficial ulcerations, nodules, or granulomas or may have an ulcerated, indurated appearance resembling carcinoma. [7 10]

Microscopic sections show a granulomatous inflammatory response to the organism. The extent of the response may vary, depending on the host's immune status and the strain of the microorganism. The yeast appears as a round-to-ovoid structure, 4 to 6 μm in diameter, surrounded by a clear halo that represents the capsule. Staining with PAS or Grocott-Gomori methenamine silver readily identifies the fungus; moreover, mucicarmine stain uniquely demonstrates its mucopolysaccharide capsule. [7 10]

Rhinosporidiosis

Rhinosporidiosis is a chronic granulomatous disease caused by a fungus called *Rhinosporidium-seeberi*, which affects chiefly the oropharynx and nasopharynx as well as larynx, skin, eyes and genital mucosa. The mode of infection is not known. The organisms appear as sporangia containing large numbers of round or ovoid endospores, each approximately 5-7 micron in diameter. In either smear preparations or tissue sections, these sporangia are characteristic. [5 7] The surrounding tissue reaction is nonspecific one, consisting of a vascular granulation tissue with focal abscess formation and occasional multinucleated giant cells. Both acute and chronic inflammatory cells are present in variable number. [5 7]

Aspergillosis

Aspergillosis is the second most common fungal infection found in humans after candidiasis. Causative pathogen is *Aspergillus fumigatus.* Incidence has increased dramatically in recent years secondary to an increase in the population of immunosuppressed individuals. Aspergillus spore is found in decaying vegetation and in the immunocompromised host. [5 7] The species also been isolated from the air and environmental surfaces of hospital settings, particularly in areas undergoing structural renovation where the hospitalized immunosuppressed individuals are at increased risk for acquiring the disease. Appearance is typically described as black or yellow necrotic lesions of the soft tissue. [5 7 10]

Tissue sections of the lesions show varying numbers of branching, septate hyphae, 3 to 4 μm in diameter. These hyphae show a tendency to branch at an acute angle and to invade adjacent small blood vessels. Occlusion of the vessels often results in the characteristic pattern of necrosis associated with this disease. [5 7 10]

Mucormycosis (Zygomycosis, Phycomycosis)

Mucormycosis is an opportunistic fungal infection caused by organisms of the class Zygomycetes, including Mucor, Rhizomucor, and Rhizopus. Can be cultured from the oral cavity, nasal passages, throat, and stools of healthy individuals. Involvement of the oral cavity is usually secondary to infection of the paranasal sinuses or nasal cavity. Clinically shows palatal necrosis or ulceration, and is noted in immunocompromised individuals. Early diagnosis and improved treatment had led to decreased morbidity and mortality. [5 10]

Histopathologic examination of lesional tissue shows extensive necrosis with numerous large (6 to 30 μm in diameter), branching, nonseptate hyphae at the periphery. The hyphae tend to branch at 90-degree angles. The extensive tissue destruction and necrosis associated with this disease are attributable to the preference of the fungi for invasion of small blood vessels. This disrupts normal blood flow to the tissue, resulting in infarction and necrosis. [5 10]

Orofacial Granulomatosis

Orofacial granulomatosis was introduced by Wiesenfeld in 1985, a well-accepted and unifying term encompassing a variety of clinical presentations. On biopsy reveal the presence of nonspecific granulomatous inflammation.[2] Previously designated as Melkersson-Rosenthal syndrome and cheilitis granulomatosa of Miescher are subsets of orofacial granulomatosis and are idiopathic but appears to represent an abnormal immune reaction to a variety of inciting agents. Majority of patients are adults however, may occur at any age. Most frequent site of involvement is lips. Labial tissues demonstrate a nontender, persistent swelling that may involve one or both lips. [11 12]

When these signs are combined with facial paralysis and a fissured tongue, the clinical presentation called Melkersson-Rosenthal syndrome. Involvement of the lips alone is called cheilitis granulomatosa (of Miescher). [5]

Histopathology

In classic cases of cheilitis granulomatosa, edema is present 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. [2 6] Scattered aggregates of noncaseating granulomatous inflammation, consisting of lymphocytes and epithelioid histiocytes, are present, with or without multinucleated giant cells. Typically, the granulomas appear to cluster around scattered vessels are not as well formed or discrete. [2 6]

Non- Specific Type

Periapical Granuloma

The term periapical granuloma refers to a mass of chronically or sub-acutely inflamed granulation tissue at the apex of a nonvital tooth. This term is not accurate because the lesion does not show a true granulomatous inflammation microscopically. [5 7]

The histopathological examination reveals an inflamed granulation tissue surrounded by a fibrous connective tissue wall. It also demonstrates a dense lymphocytic infiltrate, intermixed frequently with neutrophils, plasma cells, histiocytes, and less frequently mast cells and eosinophils. When numerous plasma cells are present, globules of gamma globulin (Russell bodies) may be seen. Epithelial rests may be identified. Collections of cholesterol clefts, with associated multinucleated giant cells and areas of red blood cell extravasation with hemosiderin pigmentation, may be present. [5 7]

Pyogenic Granuloma

These are hyperplastic lesions of granulation tissue exhibits proliferating and budding endothelial cells and fibroblasts. Clinically presentation displays the lesion is red, painless, pedunculated and relatively soft. They are usually seen on the gingiva. [5 13] Microscopically, consists of many dilated blood vessels in a loose edematous connective tissue stroma, matures with time to become more fibrous and less vascular. No true granulomas are present. Inflammation is variable, often scanty or absent. [5 13]

Peripheral Giant Cell Granuloma

Peripheral giant cell granuloma is one of the most frequent giant cell lesions of the jaw and originates from the periosteum or periodontal membrane. Not a true neoplasm but rather a benign hyperplastic reactive lesion occurring in response to local irritation or trauma. [7 13]

Histopathological examination exhibits proliferation of multinucleated giant cells (a few nuclei or up to several dozen) within a background of plump ovoid and spindle-shaped mesenchymal cells. Mitotic figures are fairly common, adjuvant with inflammatory cell infiltrate. [7 13] Abundant hemorrhage is characteristically found, which results in deposits of hemosiderin pigment, especially at the periphery. The overlying mucosal surface is ulcerated in about 50% of cases. Areas of reactive bone

formation or dystrophic calcifications are not unusual. [7]

Central Giant Cell Granuloma

Central giant cell granuloma is rarely aggressive idiopathic benign intraosseous lesion that occurs almost exclusively in the jaws. Most lesions are asymptomatic while minority of cases present with pain, paresthesia, or perforation of cortical plate resulting in ulceration of mucosal surface. [5 7 13]

Histopathologically, the lesion shows hemosiderin laden macrophages and extravasated erythrocytes along with small inconspicuous capillaries. Multinucleated giant cells are present throughout the connective tissue stroma, and may be seen in patches or evenly distributed around areas of hemorrhage. The giant cells may contain up to 30 nuclei. Foci of osteoid may be present, particularly around the peripheral margins of lesion. [7 5]

Foreign Body Granuloma

Foreign bodies or materials are the most common source of granulomatous inflammation in the oral cavity. Various foreign bodies such as wood in the orbit, impression material in the maxillary sinus, tooth fragments could be the reasons for granulomas. [2 14] The implantation of a foreign bodies results in an inflammatory reaction. They are usually too large to be phagocytosed by macrophages, the material is typically inert and does not induce an immune response. Instead, macrophages are recruited to the site for the elimination, where they become activated and are transformed into epithelioid macrophages to form a granuloma. [11 12]

Crohn's Disease

Crohn's disease is a chronic granulomatous disorder that may involve any portion of the gastrointestinal tract including the oral cavity. Microscopically there is evident of nonspecific chronic inflammation and in older lesions, there is presence of noncaseating or non-necrotizing granulomas. The etiology is unknown however, studies have shown that mutations in the CARD15/NOD2 gene on chromosome 16 up to 25% of patients with Crohn's disease. Oral manifestations are often present in patients with advanced intestinal disease.[2 12 14]

Microscopic examination of the tissue obtained from the intestine or oral mucosa shows non-necrotizing granulomatous inflammation. The severity may vary tremendously from patient to patient and from various sites. A negative biopsy result may not necessarily rule out a diagnosis of Crohn's disease. Special stains should be performed to rule out the possibility of deep fungal infection, tertiary syphilis, or mycobacterial infection. [5 7]

Langerhans Cell Disease

Langerhans cell disease, formerly known as histiocytosis X and idiopathic histiocytosis, is a spectrum of disorders characterized by a proliferation of cells exhibiting the characteristics of Langerhans cells in skin or mucosa. Demonstrated with clinical manifestations ranging from solitary to multiple bone lesions to disseminated progressive visceral skin and bone lesions. [5 7] Historically, the term histiocytosis X was used to encompass three disorders: eosinophilic granuloma, Hand-Schüller Christian syndrome, and Letterer-Siwe disease. These entities were grouped together because of their similar microscopic appearance, despite the diverse manner of clinical disease expression. [5 7]

Histopathology

Histopathologically, characterized by the proliferation of large cells with abundant cytoplasm, indistinct cell borders, and oval to reniform nuclei. These cells are often arranged in sheets, admixed with various numbers of eosinophils and other inflammatory cells. A second population of macrophages were often evident. Multinucleated giant cells and foci of necrosis may be noted. The ultrastructure shows unique, rod-shaped cytoplasmic

structures called the Birbeck granules which is also present in normal Langerhans cells. Immunohistochemical stains show the tumor cells express CD1a antigen, S-100 protein, and human leukocyte antigens (HLA)-DR. [7 8]

Wegener's Granulomatosis

Wegener's granulomatosis is a well-recognized, although uncommon disease process of unknown etiology. The initial description of the syndrome by Wegener includes necrotizing granulomatous lesions of the respiratory tract, necrotizing glomerulonephritis, and systemic vasculitis of small arteries and veins.[2 6 11] Hypotheses regarding the etiology include an abnormal immune reaction secondary to a nonspecific infection or an aberrant hypersensitivity response to an inhaled antigen. A possible hereditary predisposition has been mentioned in some cases. Before the current treatment modalities were initiated, the disorder was uniformly fatal. [6 14]

Histopathology

Wegener's granulomatosis appears as a pattern of mixed inflammation centered around blood vessels. Involved vessels demonstrate transmural inflammation, often with areas of heavy neutrophilic infiltration, necrosis, and nuclear dust (leukocytoclastic vasculitis). The connective tissue adjacent to the vessel has an inflammatory cellular infiltrate, which contains a variable mixture of histiocytes, lymphocytes, eosinophils, and multinucleated giant cells. [7 14]

Sarcoidosis

Sarcoidosis is a systemic non-necrotizing / non-caseating granulomatous disease of unknown etiology but immunological disturbance plays a major part. A multisystem disease most commonly affecting young adults. First reported in the 19th century, by Jonathan Hutchinson (1875), but the term sarcoidosis was later introduced by Boeck in 1899. [2 6] Although the etiology of is unknown, infectious agents like Mycobacterium, Propionobacteria, Epstein–Barr virus (EBV), Human herpes virus-8 (HHV-8) and environmental factors (occupational exposure) have been considered. [2 6 5]

Oral involvement appears in patients with chronic multisystem sarcoidosis and rarely occurs in the acute stage. In some cases, oral involvement is the first and only symptom of the disease. It appears as a nontender well-circumscribed brownish red or violet ceous swelling. Papules or as submucosal nodules occasionally show either superficial ulceration or be symptomatic. The diagnosis is established when clinical features are supported by histopathological evidence. [5 14]

Histopathology

Microscopic examination reveals a classic picture of granulomatous inflammation. Tightly clustered aggregates of epithelioid histiocytes are present, with a surrounding rim of lymphocytes. Intermixed with scattered Langhans' or foreign body type giant cells. The granulomas often contain laminated basophilic calcifications, known as Schaumann bodies (degenerated lysosomes) or stellate inclusions known as asteroid bodies (entrapped fragments of collagen). [5 7]

Cat Scratch Disease

Cat scratch disease is known as regional granulomatous lymphadenitis which occurs only in humans, especially those who are scratched or bitten by kittens. Primary manifestation is lymphoid hyperplasia. The disease further shows multiple granuloma formation undergoing central necrosis which coalesces to form abscess. *Bartonella henselae* is the responsible gram-negative bacillus. It is identified by PCR hybridization and indirect fluorescent antibody assay. [6]

CONCLUSION

A variety of conditions may be associated with granuloma formation in the oral cavity. Isolated granulomas may be identified from a variety of infectious and non-infectious disease processes. Because of nonspecific

clinical findings associated with these granulomatous diseases, a microscopic diagnosis often presents a diagnostic dilemma for the clinician. An extensive clinical, microscopic, and laboratory evaluation may be required to identify the source of the granulomatous inflammation.

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