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REVIEW

Giant cells and giant cell lesions of oral cavity - a review

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ABSTRACT
Giant cells are large mononucleated or multinucleated cells that are seen in a variety of physiological as well as pathological conditions. Multinucleated giant cells (MGCs) are important mediators of tissue remodeling and repair and also for removal of foreign materials and various pathogens. The commonly encountered giant cells arise from monocyte precursors, formed due to different mechanisms. Depending upon the mechanism of their formation these cells assume distinctly variable phenotypes. The giant cell lesions of oral cavity have been classified on the basis of etio-pathogenesis, the presence of which at times being pathognomic. We attempt to review the basic information regarding the mechanism of formation and morphology of giant cells and its significance in the associated giant cell lesions. Also we have tried to describe the clinical, histopathological and immunohistochemical aspects of various giant cell lesions of the oral cavity.
Keywords: Giant cell lesions of oral cavity, monocytes, multinucleated giant cells.

INTRODUCTION

A giant cell is a cell that is larger in dimension than the cells that are routinely encountered in histology. These cells are involved in many physiologic and pathological processes. The giant cells may be mononucleated or multinucleated which can be explained by the mechanism of their formation. They are easily recognized under light microscopy and hence provide a vital clue in arriving to a diagnosis. However it is essential to know the histogenesis of these unique cells, as the presence of giant cell can have a major implication on the disease process.

A multinucleated giant cell (MGCs) is a mass formed by the union of several distinct cells. They are usually of monocyte or macrophage lineage. Osteoclasts in the bones, trophoblasts in placenta, megakaryocytes in the bone marrow, etc are the physiologically present multinucleated giant cells[1]. However, in chronic inflammation when macrophages fail to deal with particles that has to be removed; fuse together and form multinucleated giant cells. Thus, their role in elimination of foreign substances, damaged tissue, and pathogens is essential for host survival. Furthermore, these cells are able to sequester irremovable materials or persistent pathogens and prevent further spread of infection.

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Monocyte/macrophages are phagocytic leukocytes that play a multitude of functional roles in the body and represent key players in both innate and acquired immune systems. Fusion of macrophages can result in the formation of osteoclasts or a variety of different MGCs, each with unique properties and tissue distributions[2]. The giant cells showing variations in their morphology and functional patterns are observed in various oral lesions. Hence it is important to know the pathogenesis of these lesions with regards to the role played by the giant cells in them.

Formation

Multinucleated giant cells were first reported in tuberculous granulomas by Rokitansky and Langhans, over a century ago[3]. It is well recognized that cells of monocyte /macrophage lineage are capable of fusion to form MGCs. However, many aspects of their recognition, adhesion, fusion, and activation, in addition to specific intercellular and intracellular signaling pathways, remain unknown[4]. These types of cells differ markedly in their association with disease states, location & prevalence in various tissues or organs; stimuli that induce the formation of the respective MGCs, and subsequent function of these cells[5].

Giant cells are found in granulomas associated with the immune response to tuberculosis, leprosy, syphilis, and various fungal and parasitic infections as well as those associated with non-immune responses to toxic agents such as silica, beryllium, and asbestos; and to non-toxic agents such as carbon particles, plastic beads, and iron particles. Since a variety of agents produce granulomas, it is thought that the giant cells are produced by different mechanisms. The two theories that were considered are:[3]

1. Amitotic division of monocyte nuclei in the absence of cellular division.
2. Fusion of non replicating monocytes.

Forkner (1930) on the basis of experiments on the blood & tissues of rabbits using different substances found that two types of giant cells were produced. The first type contained a central rosette surrounded by nuclei in the periphery. He considered it to be the epitheloid or Langhans giant cell which was formed due to nuclear division. Other group of cells with irregular arrangement of nuclei were considered to be foreign body type giant cells and thought to arise due to fusion of monocytes[6].

However, radio-labeling studies on lymph nodes of sarcoidosis patients revealed that both Langhans and foreign body giant cells arise due to fusion of monocytes and not due to “division with non disjunction”[7]. Forkner suggested that granulomas contained giant cells produced by both mechanism but were present in different proportions. He attributed the difference of opinion to be due to failure of recognition of both these types of cells[6].

Auto-radiographic studies on the formation of giant cells revealed that giant cells indeed form due to fusion[3] which has been supported by other authors also[2,7]. In general, cell fusion results from an alteration of cell surface which allows close membrane approximation, followed by establishment of continuity between the apposed lipid bilayers[8]. The process of fusion can occur due to a variety of mechanisms[9]. Firstly, an immune mediated phenomenon has been proposed for the formation of giant cell. Here large amount of lymphokines are produced that causes fusion of macrophages to form multinucleated giant cells[10]. Macrophage MGCs are commonly found in areas containing poorly removable foreign material which are antigenic (microorganisms). Even when the foreign material itself has no antigenicity (Eg: Glass) it is possible that the inflammatory process itself produces antigen which is responsible for macrophage fusion[11].

Secondly, it was also proposed that fusion occurs between "young" macrophages and "older" cells, the latter having existed for some time in the granulomatous environment acquiring chromosomal abnormalities and changes on macrophage surface. The recognition of altered and abnormal cell surface by young macrophages is the stimulus for cell fusion, and the process is regarded as a means whereby altered, effete and senescent cells can be removed[12]. A third mechanism proposed, suggested that when two or more macrophages try to ingest the same particle, there is simultaneous attempted phagocytosis resulting in the fusion of endosomal margins to form multinucleated giant cells[9].

The role of viruses in fusion of many cell types throughout the body, including macrophages has been explained. Fusion may be achieved by large doses of inactivated virus or by much smaller doses of infective virus[13]. With inactivated virus there appears to be a direct interaction between the viral envelope and cell surface. Attachment of viral envelope leads to the reduction in cell coat thickness and fusion with the cell membrane. Cell fusion results if the virus is in contact with more than one cell. Antigens from the viral envelope become incorporated into the polykaryon membrane[14], resulting in the fusion between the two cells by forming a "bridge". Live virus penetrates a cell and leads to fusion following the appearance of virally coded proteins on the cell surface. The infected cell thus has a surface modified by viral proteins which leads to fusion with adjacent uninfected cells. Fusion extends in a plaque to form an expanding syncytium[5,8].

Types of giant cells

Multinucleated giant cells can be classified into several morphological variants (Figure 1)[2] depending on the arrangement and composition of their organelles, as well as their functional characteristics[2]. Osteoclasts, odontoclasts, skeletal muscle fibers, syncytotrophoblasts and megakaryocytes are the physiologically present multinucleated giant cells. Few of these also have a role to play in various pathological processes[1].

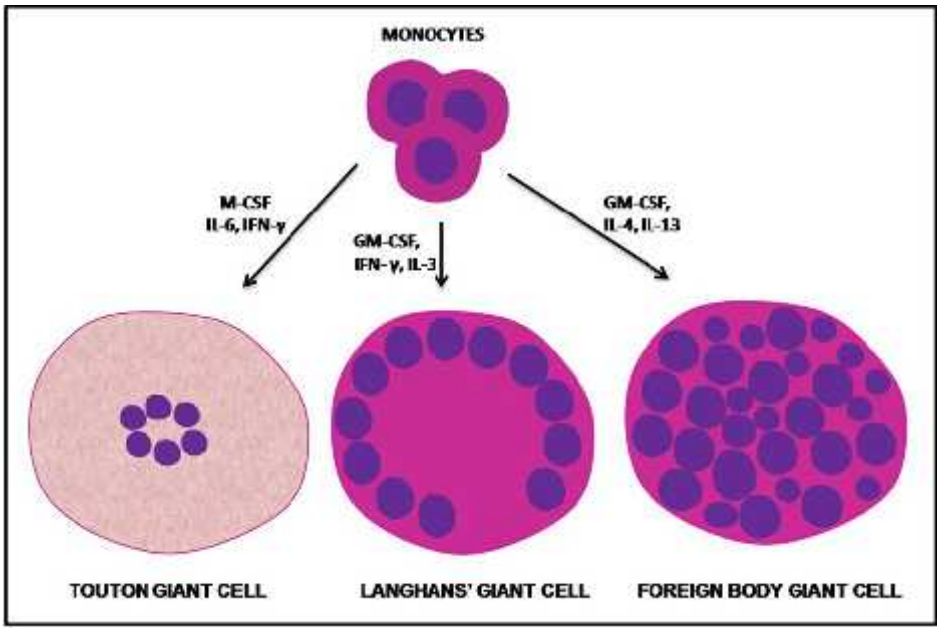

Figure 1. Morphological variants and factors stimulating formation of multinucleated giant cells.

Osteoclasts

Osteoclasts, as named by Kolliker are bone-resorbing cells that play a pivotal role in bone homeostasis and remodeling. Osteoclast precursors are derived from bone marrow as early mononuclear macrophages, which circulate in blood, and bind to the surface of bone[15].

Osteoclast formation is driven mainly by two cytokines, Receptor Activator of Nuclear Factor Kappa β Ligand (RANKL) and macrophage - colony stimulating factor (M-CSF)[15]. In addition a wide variety of factors like systemic hormones and growth factors influence the formation and function of osteoclasts. Morphologically, osteoclasts are similar to foreign body giant cells, although they have considerably fewer nuclei[2]. They usually contain 10 to 20 nuclei per cell and are found on bone surfaces; on the endosteal surfaces within the haversian system; and on the periosteal surface beneath the periosteum[1]. The osteoclastic giant cells show positivity to cathepsin K, alkaline phosphatase, RANKL, osteoprotegerin & Cluster of Differentiation 68 (CD68)[15]. The calcitonin receptor is found to be a more specific marker of differentiation for osteoclasts from other giant cells derived from monocyte/ macrophage cell lineage[5].

Tumor giant cells

Many epithelial and mesenchymal neoplasms contain tumor giant cells[16]. The nuclei of these giant cells are pleomorphic, often diploid, shows abnormal mitosis and resemble those of mononuclear tumor population[8]. Tumor cells are known to possess an abnormal surface and are predisposed to fusion in different ways[17]. Many tumors have been shown to release extracellular enzymes[18] which may reduce the surface coat thickness and cause close approximation of lipid bilayers leading to fusion. Some tumors have been found to be associated with passenger viruses, which are known to cause cell fusion[8]. Josten M & Rudolph R have differentiated the giant cells in canine and feline neoplasia using Mindbomb homolog 1 (MIB1) & tartrate resistant acid phosphatase (TRAP). The study showed that the neoplastic giant cells showed positivity for MIB1 but not for TRAP, suggesting that neoplastic giant cells have a different phenotype than osteoclasts[19].

Touton giant cells

Touton giant cells are characterized by multiple nuclei that cluster together in the cell and are surrounded by foamy cytoplasm[2]. These cells were originally known as xanthelasmatic giant cells and are formed by fusion of macrophage derived foam cells[20]. These MGCs are most frequently found in lesions containing cholesterol and lipid deposits, and are associated with various pathologic processes, such as xanthomas and xanthogranulomas[21]. Touton types of giant cells are appreciated in cases of fibrous histiocytoma[22]. The lipid droplets in the cytoplasm of these cells can be demonstrated in frozen section by special stains[23]. Lysozyme, α1 antitrypsin, CD68 & factor XIIIa can be used as a marker for differentiation of these multinucleated giant cells[21].

Langhans' giant cells

Langhans' giant cells are characterized by the presence of few nuclei (< 20) arranged peripherally, within the giant cell. They are commonly found in immune granulomas and granulomatous inflammations in the presence of indigestible particles of organisms, eg: the tubercle bacillus. The presence of MGCs in the tuberculous granuloma was first described by Langhans in 1868. Interferon-gamma (IF-γ) plays a central role in inducing Langhans' giant cell formation[5]. These cells show positivity to CD68[24]. It has also been seen that larger the size and more the number of nuclei in MGCs, the virulence of disease increases. Lay et al

have shown that high virulence mycobacterium, i.e., *Mycobacterium tuberculosis*, induces large MGCs with more than 15 nuclei per cell, whereas low-virulence mycobacterium species, *Mycobacterium avium* and *Mycobacterium smegmatis*, have low number of nuclei per cell, less than seven. Of special note is that the high-virulence mycobacterium species resulted in granulomas where the MGCs phagocytic activity was absent, as opposed to the low-virulence species that produced MGCs where phagocytic activity was present[25].

Foreign body giant cells

Foreign body giant cells (FBGCs) are generated by macrophage fusion and serve the same purpose as osteoclasts: degradation/resorption of the underlying substrate. Unlike osteoclasts, which adhere to bone, FBGCs, together with their macrophage precursors, adhere to markedly different synthetic surfaces that display distinct differences in hydrophilic/hydrophobic character as well as chemical and physical properties[15]. FBGCs contain many nuclei (up to 100 - 200) that are arranged in a diffuse manner throughout the cytoplasm[2].

Foreign body giant cells are observed at the tissue-material interface of medical devices implanted in soft and hard tissue and remain at the implant-tissue interface for lifetime, of the device *in vivo*. In addition, FBGCs have also been implicated in the biodegradation of polymeric medical devices. FBGCs and macrophages constituting the foreign body reaction at the tissue-device interface are surface area dependent. Fabrics utilized as vascular grafts show high densities of FBGCs, whereas flat surfaces such as those found on breast implants exhibit only one to two cell layer[15].

Human immunodeficiency virus-1 (HIV-1) mediated syncytium formation, Warthin Finkeldey cells, Reed Sternberg cells are the other multinucleated giant cells associated with HIV, Rubeola and Hodgkins lymphoma; respectively[26,27].

Giant cell lesion of oral cavity

Giant cell lesions of oral cavity can be cystic, neoplastic, microbial, etc. For proper diagnosis and management of giant cell lesions, it is necessary to know about the pathogenesis of disease and the nature of giant cells. Giant cell lesions of oral cavity have been classified based on the etiopathogenesis as described by Chattopadhyay A (1995)[28] (Table 1) and Varghese et al (2011) as follows[29].

Classification

1. Microbial lesions
   a. Tuberculosis
   b. Leprosy
   c. Actinomycosis
   d. Sarcoidiosis
2. Tumor and tumor like lesion
   a. Central giant cell granuloma
   b. Peripheral giant cell granuloma
   c. Giant cell fibroma
   d. Osteosarcoma
   e. Rhabdomyosarcoma
   f. Hodgkins lymphoma
3. Cystic lesion
   a. Traumatic bone cyst
   b. Aneurysmal bone cyst
4. Metabolic lesion
   a. Hyperparathyroidism
5. Osteodystrophic lesion
   a. Noonan-like multiple giant cell lesion syndrome
6. Miscellaneous lesion
   a. Cherubism
   b. Paget's disease
   c. Fibrous dysplasia

Oral Tuberculosis

Tuberculosis (TB) is a specific infectious granulomatous disease caused by *Mycobacterium tuberculosis*[24]. Tuberculous lesions of oral cavity may be primary or secondary to pulmonary

Table 1. Classification of giant cell lesions of oral cavity based on the pathogenesis.

Lesions where giant cells in the concerned background are pathognomic	**Lesions where giant cells are characteristic but not pathognomic**	**Lesions associated with presence of giant cell**
Hodgkins lymphoma	Tuberculosis	Orofacial granulomatosis, fungal infection, foreign body reaction, neoplasm, syphilis, leprosy, fibrous dysplasia, cherubism, ossifying fibroma, aneurysmal bone cyst, paget's disease of bone, wegners granulomatosis actinomycosis, odontogenic giant cell fibromatosis
Peripheral/central giant cell granuloma	Herpes Simplex Virus infection	
	Measles	
Giant cell fibroma	Xanthoma	

tuberculosis[30]. Primary tuberculosis occurs in previously unexposed people and mostly involves the lungs where as secondary tuberculosis occurs from a reactivation of organism in a previously infected person, typically associated with compromised host defenses. Although tongue is the commonest site for oral tuberculous lesions[31], they may also occur on gingiva, floor of mouth, palate, lips and buccal mucosa[32]. The typical oral lesions consist of a stellate ulcer with undermined edges and a granulating floor[33]. The characteristic histopathologic appearance is due to cell-mediated hypersensitivity reaction. Formation of granuloma exhibiting foci of caseous necrosis surrounded by epitheloid cells, lymphocytes, and occasional multinucleated giant cells are seen. Langhans' giant cells are seen, the presence of which is not diagnostic but indicative of tuberculosis. The diagnosis of tuberculosis is confirmed by the presence of acid fast bacilli in the specimen or culture of sputum[24].

Oral leprosy

Leprosy is a chronic multi-systemic disease caused by acid fast, rod shaped bacilli *Mycobacterium leprae*, wherein the clinico-pathological presentation is determined by the complex interaction between the invading organism and immune status of the individual[34]. Involvement of oral cavity in leprosy is variable, seen in 19-60% of the patients,[35] with involvement being more common in multibacillary disease compared to paucibacillary[36]. Hard palate is the most frequent site of oral involvement, followed by soft palate, labial maxillary gingiva, tongue, lips, and buccal mucosa, correlating with their lower mean surface temperatures[37] around 1-2^{0}C less than body temperature[38]. The spectrum of oral lesions may vary from relatively non specific like enanthem to more specific lesions like papules, nodules and ulcers showing bacillary positivity[39]. Involvement of lip may result into cheilitis granulomatosa[39]. Gingival hyperplasia with loosening of teeth has also been reported. The typical granulomatous nodule shows collections of epitheloid histiocytes and lymphocytes in a

fibrous stroma. Langhans' type giant cells are variably present[24].

Oral actinomycosis

Actinomycosis is a chronic suppurative soft-tissue infection caused by *Actinomyces israelii*, which are filamentous, gram-positive, non acid-fast, anaerobic to microaerophilic bacteria that live as commensal organisms in the oral cavity, respiratory and digestive tracts[40]. Clinical manifestations of actinomycosis occur in three areas: cervicofacial (50%), abdominal-pelvic (23%), and thoracic (17%)[41]. Suppurative reaction of the infection may discharge large yellowish flecks that represent colonies of bacteria called sulphur granules. Cervicofacial actinomycosis affects the areas of prior trauma, due to soft tissue injury, periodontal pocket, non vital tooth, extraction socket or infected tonsil. Histopathologically a central abscess formation with colonies of microorganisms floating in a sea of polymorphonuclear leukocytes is observed, often associated with multinucleated giant cells and macrophages particularly around the periphery of the lesion[24]. The diagnosis is usually made by fine-needle aspiration biopsy followed by observing actinomycosis colonies or sulfur granules in microscopic examination[42].

Oral Sarcoidosis

Sarcoidosis, in Greek meaning "flesh like condition"[43] is a systemic non caseating granulomatous disease of unknown etiology, although genetic, infectious and environmental factors have been postulated as possible cause. The most common presentation consists of pulmonary infiltration and hilar lymphadenopathy; dermal and ocular lesions[44]. When the parotid glands are affected, 4-6% of cases present as parotitis and Heerfordt syndrome[45].

Histopathology of sarcoidosis will show non caseating granulomas, the center of which usually contains epitheloid macrophages surrounded by a rim of lymphocytes[46]. Langhans type giant cells resulting from the fusion of epitheloid mononuclear cells, occasionally containing many inclusion bodies such as Schaumann bodies or stellate asteroid bodies are observed[47]. Corticosteoids have remained as the mainstay in treatment of sarcoidosis although with a chance of around 70% relapse within a two years period[48].

Central giant cell granuloma

Central giant cell granuloma (CGCG) was classified by the World Health Organization in 2005 as a rarely aggressive idiopathic benign intraosseous lesion that occurs almost exclusively in the jaws[49]. Most lesions are asymptomatic while minority of cases present with pain, paraesthesia, or perforation of cortical plate resulting in ulceration of mucosal surface. Histopathologically, CGCG shows hemosiderin laden macrophages and extravasated erythrocytes along with small inconspicuous capillaries[50]. Multinucleated giant cells are present throughout the connective tissue stroma, and may be seen in patches or evenly distributed around areas of haemorrhage. The giant cells contain up to 30 nuclei[51]. Foci of osteoid may be present, particularly around the peripheral margins of lesion[50]. CGCG shares overlapping histological features with aneurysmal bone cyst (ABC), browns tumor of hyperparathyroidism, giant cell tumors of bone & cherubism and should therefore be carefully evaluated[51].

Peripheral giant cell granuloma

Peripheral giant cell granuloma (PGCG) is one of the most frequent giant cell lesion of the jaws and originates from the periosteum or periodontal membrane. It is not a true neoplasm but rather a benign hyperplastic reactive lesion occurring in

response to local irritation such as tooth extraction, poor dental restorations, ill-fitting dentures, plaque, calculus, food impaction and chronic trauma[52]. Histopathologically, fibroblasts are the basic element of peripheral giant cell granulomas. Other features include a non-encapsulated highly cellular mass with abundant giant cells, inflammation, interstitial hemorrhage, hemosiderin deposits, mature bone or osteoid. Scattered among the plump, young fibroblasts are numerous multinucleated giant cells with abundant eosinophilic cytoplasm which appear to be non-functional in the usual sense of phagocytosis and bone resorption[53]. Management of this gingival lesion is surgical excision and elimination of any local contributing factors[54].

Giant cell tumor of bone

Giant cell tumors (GCTs) are benign bone tumors arising from bone marrow, which account for about 5% of all biopsied primary bone tumors. The head and neck region constitute approximately 2% of all GCTs, with the majority occurring in sphenoid, ethmoid, or temporal bones[55]. Radiologically, it is usually lytic and expansile without prominent peripheral sclerosis and periosteal reaction[56]. The histopathology of GCTs is characterized by frank and marked haemorrhage, numerous giant cells and stromal cells. The haemorrhage gives rise to the characteristic grossly lytic picture. The giant cells are considered reactive while stromal cells are considered "true" neoplastic cells. The giant cells are thought to be originating from circulating monocytes which then transform into osteoclasts[56]. Treatment includes simple or aggressive curettage. Tumor resection and reconstruction with prosthesis or a large segment allograft has a low rate of local recurrence[57].

Giant cell fibroma

Giant cell fibroma (GCF) is a relatively rare fibrous hyperplastic lesion that is considered to occur due to chronic irritation. It is characterized by functional changes in the fibroblastic cells[58]. Giant cell fibroma occurs as an asymptomatic sessile or pedunculated nodule, usually less than 1 cm in size affecting mandibular gingiva twice as common as maxillary. Histopathologically, the lesions are characterized by a diffuse, somewhat immature, rather avascular collagenic stroma with small bipolar and slightly stellate fibroblasts scattered throughout in moderate numbers. Occasional fibroblasts will be quite large and angular, and may have more than one nucleus. GCF is characterized by the presence of numerous large stellate and multinucleated giant cells in a loose collagenous stroma[59]. The giant fibroblasts are negative for CD68 but show positivity for vimentin[60].

Giant cell angiofibroma

Giant cell angiofibroma (GCA) is a distinctive benign, mesenchymal tumor commonly encountered in the orbit. It has been reported to occur in submandibular region, parascapular area, posterior mediastinum and in the oral cavity[61]. It presents as a slow growing nodule or mass with normal overlying mucosa[62]. Histopathologically, is characterized by a richly vascularized, patternless spindle-cell proliferation containing pseudovascular spaces. Multinucleated giant cells (often of floret type) and cells with large, rounded nuclei are present both in the cellular areas and also lining the pseudovascular spaces. The stroma is variably collagenized or sometimes myxoid[63]. Immunohistochemically, the spindle and giant cells are positive for both vimentin and CD34[63].

Hodgkin's lymphoma

Hodgkin's lymphoma is a malignant lymphoproliferative disorder which affects primarily lymph nodes with secondary extranodal spread[29]. Hodgkin lymphoma (HL) most frequently presents as cervical

lymphadenopathy and rarely involves extranodal sites. The seldomly reported lesions include different locations: palate, tonsil, floor of mouth, buccal alveolar mucosa, buccal vestibule, and mandibular bone, with no one site accounting for a predominance of cases. The more commonly described clinical presentations are ulcerations and swellings[64]. For the diagnosis of Hodgkin's lymphoma the presence of Reed Sternberg cells must be established. This cell of lymphocytic origin is characterized by its large size and bilobed nucleus; each containing a large amphophilic or eosinophilic nucleolus. The nuclear chromatin pattern is vesicular and condensed at the periphery[62]. Reed Sternberg cells may be lacunar, polyploid or pleomorphic[24]. Treatment includes cytotoxic drugs, immunotherapy and radiotherapy. High dose chemotherapy and autologous stem cell transplantation has also become an established mode of treatment[65].

The prognosis of the disease can be related to the number of giant cells. The lymphocyte depletion type of Hodgkin's lymphoma which has the most abundant Reed Sternberg cells shows the least favorable prognosis[62].

Aneurysmal bone cyst

Aneurysmal bone cysts are non-neoplastic benign bony lesions with multilocular appearance[66]. When present in the jaw, these manifest as a swelling which develops rapidly. Pain is often reported; paraesthesia, compressibility, and crepitus are rare[27]. According to Hillerup and Hjorting-Hansen, an intra-medullary haematoma secondary to trauma, may be the causative factor for the development of ABC[66]. Microscopically, numerous cavernous, sinusoidal spaces filled with blood are surrounded by loose, fibrous connective tissue. The connective tissue septa contain small capillaries, multinucleated giant cells, inflammatory cells, extravasated erythrocytes, and hemosiderin. The multinucleated, osteoclast-like giant cells often aggregate adjacent to the sinusoidal spaces[67]. There are various treatment options suggested in the literature ranging from percutaneous sclerotherapy, diagnostic and therapeutic embolization, curettage, block resection and reconstruction, radiotherapy and systemic calcitonin therapy. Self healing cases have also been reported on long term follow up[68].

Liu et al in their study to compare the histopathology of giant cell lesions of jaw found out that MGCs have similar morphology and distribution among giant cell granuloma, cherubism and aneurysmal bone cyst. Under immunohistochemical and in-situ hybridization study the giant cells were positive for TRAP and osteoprotegerin, indicative of osteoclast phenotype[69].

CONCLUSIONS

Multinucleated giant cells are commonly encountered in various lesions of oral cavity. They may be characteristic for the lesion or exist just as a reactive process, related to the elimination of microbes or foreign materials. Nonetheless, they provide a vital clue to the diagnosis. Although, various theories have been put forward to explain the genesis of the multinucleated giant cells, the exact mechanism still remains enigmatic and interesting. So a definite criterion to identify individual giant cells in any giant cell lesions however is required to assist the clinician and researchers for proper diagnosis and management.

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