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GIANT CELL: TAKE A LOOK

Dentistry

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ABSTRACT

Giant cells are large cells that often contain more than one nucleus and appear as a merger of several distinct cells. They are derived from multiple lineages, but are usually of monocyte or macrophage origin. These cells can be seen either in physiologic or in pathologic conditions. Osteoclasts in the bones, trophoblasts in placenta, megakaryocytes in the bone marrow are the physiologically present multinucleated giant cells. However, in common pathological states such as chronic inflammation when macrophages fail to deal with particles that has to be removed; they fuse together and form multinucleated giant cells. Thus, their role in elimination of foreign substances, damaged tissue and pathogens is essential for host survival. Multinucleated giant cells can be classified into several morphological variants depending on the arrangement and composition of their organelles, as well as their functional characteristics. These variants include FBGC, Langhans giant cells, Touton giant cells, osteoclasts and osteoclast-like cells. Since most of the giant cell variants are derived from monocyte/macrophage precursors, their morphological and functional heterogeneity seems to be determined by the specific tissue location and local factors present in the milieu where cell fusion occurs.

KEYWORDS

Giant cells, multinucleated cells, osteoclasts.

INTRODUCTION

Cell is defined as the fundamental, structural & functional unit of all known living organisms. The term "cell" was coined by Robert Hooke. It is derived from the Latin word "cellula" which means small compartment. Cells usually contain a single nucleus[1]. But certain tissues contain cells in which several nuclei are present within the same cytoplasm they are termed as multinucleated giant cells[2]. These cells were first reported in tuberculous granulomas by Rokitansky and Langhans over a century ago.[3]Giant cells are large multinucleated cells of different lineage and the lesions containing giant cells fascinate clinicians, radiologists and pathologists.[4]

Multinucleated giant cells are morphologically characterized by the presence of multiple nuclei dispersed in cytoplasm. Multinucleated cells are commonly encountered in oral and maxillofacial lesions. An epidemiological study by Mohajerani et al. has reported that 6.36% of the oral biopsies received in their laboratory were lesions containing multinucleated giant cells. Classifying oral lesions with giant cells has always been problematic.[5] Traditionally, giant cell lesions of oral cavity has been classified with little importance based on the type or histogenesis of multinucleated giant cells present in the lesions.[6] Giant cells are of many different types and occur under different conditions and assume different configurations. They are formed by fusion of macrophages and are common in granulomatous inflammation, especially in infections such as tuberculosis, syphilis and those produced by fungi. Reaction to exogenous substances such as keratin, fat and cholesterol crystals is also commonly the cause of the development of giant cells[3].

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 (multinucleated giant cells), each with unique properties and tissue distributions.[7] However, many aspects of their recognition, adhesion, fusion, and activation, in addition to specific intercellular and intracellular signaling pathways, remain unknown.[8],[9,10]

DISCUSSION

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. Many epithelial and mesenchymal tumors show multinucleated giant cells in their histology. Some of these giant cells are pathognomonic for the tumors while others are often as a result of defective cell divisions occurring as a consequence of anaplasia.[11] Formation of multinucleated giant cells in malignancies can be attributed to the newly discovered cellular events in tumor cells like mitotic catastrophe. The growth of malignant tumor cells that have accumulated mutations and genomic material (aneuploid) often evokes an onco suppresive cellular mechanism called mitotic catastrophe. This event is characterized by unique nuclear alterations, resulting in the formation of multinucleated giant cells.[12] Giant cell lesions in the oral tissues occur as intraosseous growth within the jaw and as extra bony lesions in the soft tissue.

The soft tissue giant cell lesion is the giant cell epulis or peripheral giant cell granuloma. Giant cells are pathognomonic features of some lesions like central and peripheral giant cell granuloma giant cell fibroma, Hodgkin's lymphoma, etc. There are some lesions where giant cells are the characteristic features but not the pathognomonic feature as in tuberculosis, measles, xanthomas, HSV infection, etc. There are certain lesions where giant cells are present like orofacial granulomatosis, fungal infection, foreign body reactions, neoplasms, syphilis, leprosy, fibrous dysplasia, Cherubism, ossifying fibroma, aneurysmal bone cysts, Paget's disease of bone, Wegener's granulomatosis, actinomycosis, chronic diffusing sclerosing osteomyelitis, Heerfordt syndrome, odontogenic giant cell fibromatosis, measles.[13]

Multinucleated giant cells are commonly encountered in various lesions of oral cavity. These giant cell containing lesions have overlapping histopathological features which need to be differentiated from each other.[14]

Formation of giant cell

Singer and Nicolson (1872)[23]stated that the cell membrane consists of a lipid bilayer in which the protein floats with varying degrees of lateral mobility. This lipid layer needs to be reconditioned by some destabilizing process so that it can fuse with other bilayer.

Harris (1968)[24]has shown that nuclear division in a polykaryon is normally followed by the formation of a single mitotic spindle, leading to the production, not of more nuclei, but a single hyperdiploid nucleus.

Heine and Schnaitman (1971)[11]suggested that the antigens from the viral envelope becomes incorporated into the polykaryon membrane showing that the fusion results from the viral envelope forming a bridge between two cells.

Marino and Spector (1974)[25] have presented evidence that this sequence applies in at least one polykaryon in vivo, the macrophage giant cell.

Three mechanisms are put forth to explain the fusion:

1. Fusion mediated by immune system:

Lymphokines and membrane changes on the cell will facilitate the adherence and fusion of macrophages.

2. Fusion from recognition of an abnormal macrophage surface by young macrophage: Chromosome abnormalities lead to the formation of an abnormal cell surface. This is recognised by fresh/ young macrophage and fusion occurs.

3. Fusion due to endocytic activity:
An endosome margin is formed when antigen attaches to the surface of the macrophage. One endosome margin fuses with the other and fusion takes place.[23]

It is a complex process induced by –
Cytokines IL4, GM-CSF – Foreign Body Giant Cell Formation
INF-GAMMA, IL3 – Langhans Giant Cell Formation

Adhesion Molecules: Beta – Intigrins, CD36, CD44, Cd200

NADPH Oxidase: Generates Reactive Oxygen Species (ROS) And Play An Important Role In Macrophage Fusion.

Morphological variants and factors stimulating formation of multinucleated giant cell

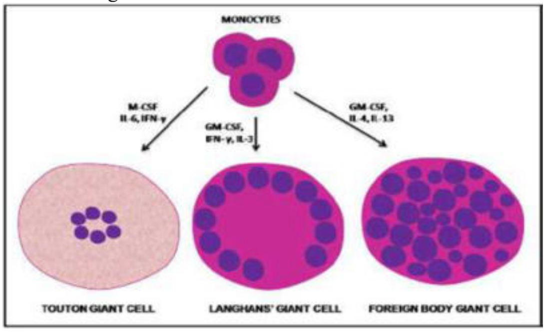

FIG1: Morphological variants and factors stimulating formation of multinucleated giant cell

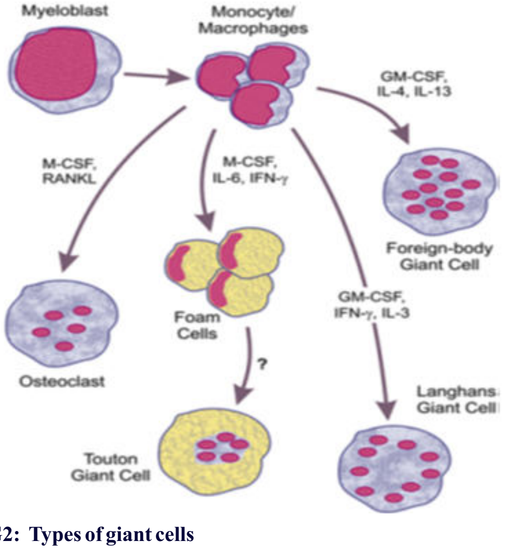

FIG2: Types of giant cells

High levels of matrix metalloproteinase (MMP -9) during macrophage fusion in vitro and in foreign body giant cells (FBGCs) in vivo.[26] Protein kinase C may play an important role in the formation of macrophage-derived MGC.[27] Osteoclasts and foreign body giant cells have revealed a number of common factors, for example, vitronectin, an adhesion protein, dendritic cell-specific transmembrane protein (DC- STAMP), a fusion factor, and macrophage fusion receptor, that contribute to giant cell formation and function. Among the cytokines that have been found to induce or benefit monocyte fusion, IFN-γ has a prominent role.[28]

TYPES

Osteoclasts
Tumor giant cells
Touton giant cells
Langhans giant cells
Foreign body giant cells

OSTEOCLASTS

Osteoclasts 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. Osteoclast formation is driven mainly by two cytokines, Receptor Activator of Nuclear Factor Kappa β Ligand (RANKL) and macrophage - colony stimulating factor (M-CSF). 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. 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. The osteoclastic giant cells show positivity to cathepsin K, alkaline phosphatase, RANKL, osteoprotegerin & Cluster of Differentiation 68 (CD68)[30]. 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.[30]

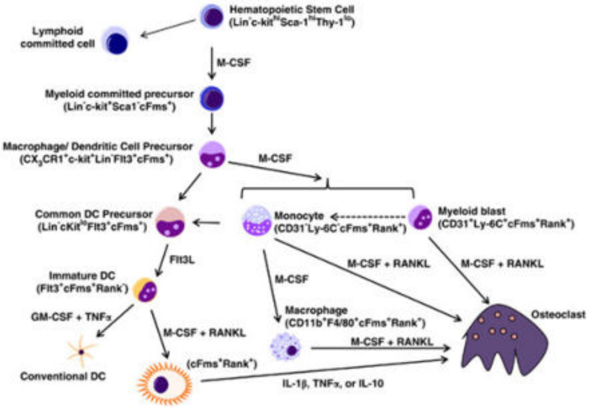

FIG3: Osteoclast precursor development and differentiation

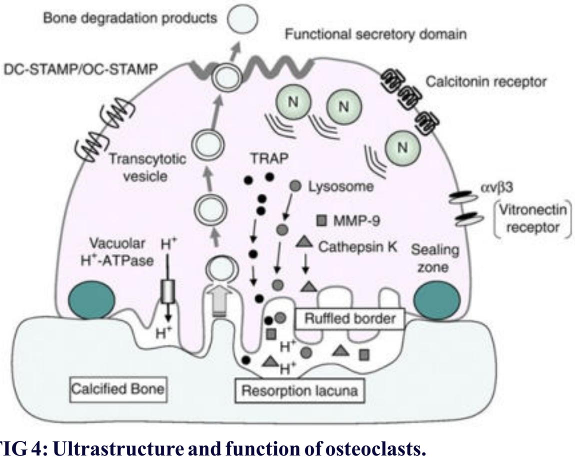

FIG 4: Ultrastructure and function of osteoclasts.

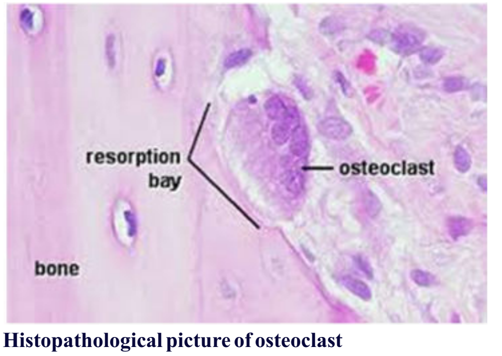

FIG5 Histopathological picture of osteoclast

TUMOR GIANT CELLS

Many epithelial and mesenchymal neoplasms contain tumor giant cells[32]. The nuclei of these giant cells are pleomorphic, often diploid, shows abnormal mitosis and resemble those of mononuclear tumor population.[2] Tumor cells are known to possess an abnormal surface and are predisposed to fusion in different ways. Many tumors have been shown to release extracellular enzymes which may reduce the surface coat thickness and cause close approximation of lipid bilayers leading to fusion[2]. Some tumors have been found to be associated with passenger viruses, which are known to cause cell fusion. **Josten M& Rudolph R** have differentiated the giant cells in canine and feline neoplasia using Mind bomb 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.

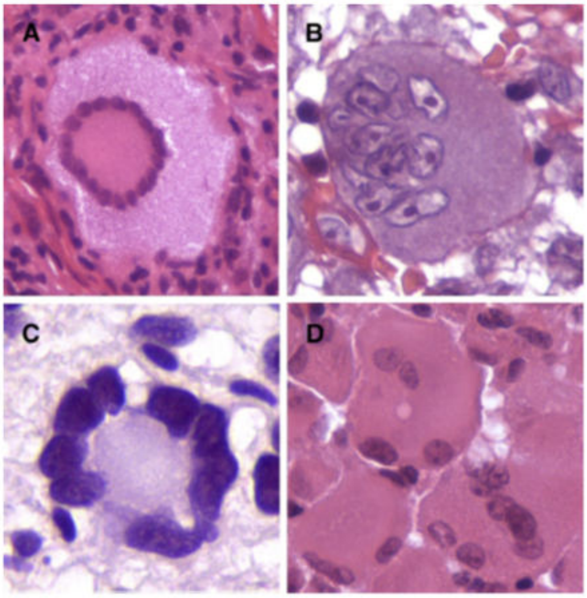

FIG6(A)Touton. (B) Osteoclast-like. (C) Floret-like. (D) Glassy.

TOUTON GIANT CELLS

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

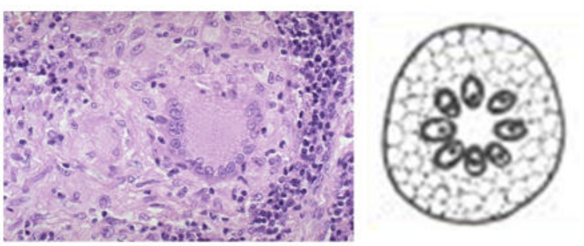

FIG 7 Touton Giant Cells

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. These cells show positivity to CD68. 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.[17,18]

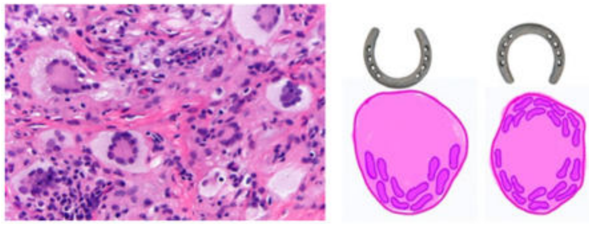

FIG 8: Langhans' Giant Cells

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.[30] FBGCs contain many nuclei (up to 100 - 200) that are arranged in a diffuse manner throughout the cytoplasm.[20] 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.[30]

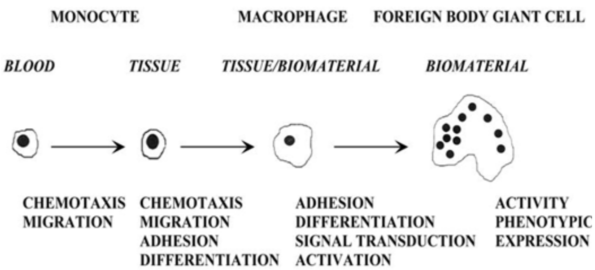

FIG 9: In vivo transition from blood-borne monocyte to biomaterial adherent monocyte/macrophage to foreign body giant cell at the tissue/biomaterial interface. There is ongoing research to elucidate the biological mechanisms that are considered to play important roles in the transition to foreign body giant cell development.

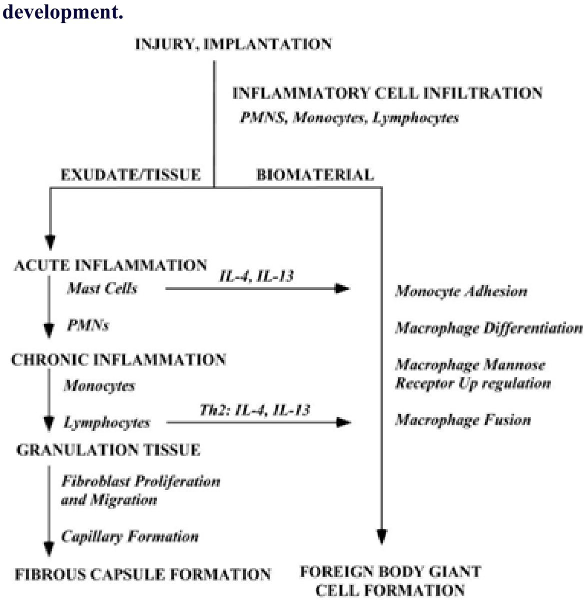

FIG10: Sequence of events involved in inflammatory and wound healing responses leading to foreign body giant cell formation.

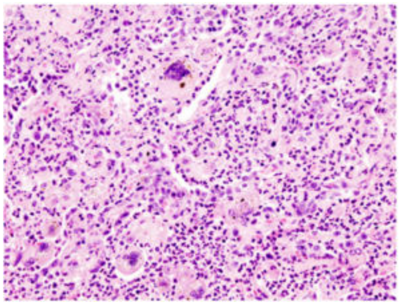

Fig10 (a) Foreign Body Cells

CONCLUSION

The giant cell lesions of oral cavity have been classified on the basis of etio-pathogenesis, the presence of which at times being pathognomic like in Hodgkin's disease, peripheral giant cell granuloma and giant cell fibroma. Also, there are conditions like tuberculosis, herpes simplex virus infection, measeles and xanthomas where giant cells are characteristic but not pathognomic. Diseases like orofacial granulomatosis, fungal infections, fibrous dysplasia cherubism, Paget's disease of bone are also associated with the presence of giant cells. A variety of oro-facial lesions contain multinucleated giant cells. Some giant cells forming within the body are pathognomic and some are not pathognomic of their respective lesions. For example, in giant cell lesions like Hodgkins's lymphoma, peripheral and central giant cell granulomas and giant cell tumor the multinucleated giant cells are found to be pathognomic. In lesions like tuberculosis, HIV, measles, xanthoma multinucleated giant cells are characteristic but are not pathognomic.

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