Giant Cells : An Overview !!!

Article · July 2020

CITATIONS
0

READS
4,230

1 author:

Saurabh Nagar
Tata Memorial Centre
21 PUBLICATIONS **39** CITATIONS

SEE PROFILE

Review Article

Giant Cells : An Overview !!!

Dr. Saurabh R. Nagar [M.D.S.][1], **Dr. Tabita Joy** [M.D.S.][2], **Dr. Manisha S. Ahire (Sardar)** [M.D.S.][3], **Dr. Anuradha Sinha** [M.D.S.][4], **Dr. Zaneta Ivy D'souza** [B.D.S.][5], **Dr. Vivek Pakhmode** [M.D.S.][6]

1) Assistant Professor, Dept. Of Oral Pathology & Microbiology, Government Dental College & Hospital, Mumbai, India.
2) Associate Professor & HOD, Dept. Of Oral Pathology & Microbiology, Government Dental College & Hospital, Mumbai, India.
3) Associate Professor (Academic), Dept. Of Oral Pathology & Microbiology, Government Dental College & Hospital, Mumbai, India.
4) Assistant Professor, Dept. Of Oral Pathology & Microbiology, Government Dental College & Hospital, Mumbai, India.
5) Post-graduate student, Dept. Of Oral Pathology & Microbiology, Government Dental College & Hospital, Mumbai, India.
6) Joint Director, Directorate of Medical Education & Research, Dean, Government Dental College & Hospital, Mumbai, India.

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. Depending upon the tissue where fusion occurs and the inflammatory result, multinucleated giant cells assume distinctly different phenotypes. Present review aims to concisely explain giant cells with its significant role in different physiological and pathological conditions which would be helpful in diagnosis and treatment plan of various entities which shows giant cells.

Keywords: Giant Cells; Macrophages; Phagocytosis; Multinucleated cells.

Address for Correspondence

Dr. Saurabh R. Nagar [M.D.S.]
Assistant Professor,
Dept. Of Oral Pathology & Microbiology,
Government Dental College & Hospital,
Mumbai-400001, Maharashtra, India.
Email id : saurabh.nagar90@gmail.com
Phone Number : +91 9819865007

Introduction

"**Giant**" is the English word coined in 1297 commonly used for such beings which are very large when compared to normal.[1] According to The American Heritage Medical Dictionary Giant cell is defined as "an unusually large cell, especially a large multinucleated phagocytic cell. A giant cell is a mass formed by the union of several distinct cells (usually macrophages) which undergo a defined set of intercellular interactions that ultimately result in a multinucleated cell with a single cytoplasmic compartment. There are two types pathologic and physiologic giant cell. (Creighton).[2]

Muller J[2] had discovered giant cells. Virchow and Langhans[3] discussed their nature. Lambert A[3] observed the formation of multinucleate giant cells from wandering mononuclear cells, while Lewises reported the transformation of the mononuclear blood cells of lower vertebrates into giant cells in hanging drop cultures. However giant cells are not always multinucleate they may be also uninucleate, its just their large size which designates them as giant cells. This review presents concise information of classification, formation, cell of origin and description of different types of giant cells which would be helpful in diagnosis and treatment plan of various entities which shows giant cells.

among which the most recent classification is as follows -

Based on type: Mathew et al 2016[5]

i) Epithelial-derived viral - induced multinucleated giant cell containing lesions

   tzank giant cells – herpes simplex

   tzank giant cells – herpes zoster

ii) Monocyte/ multinucleated giant cell containing lesions

   A. Inflammatory granuloma associated giant cells

      - Langhans giant cell containing pathologies : infections – tuberculosis, leprosy, late syphilis, deep fungal infections;

      unknown antigenic stimuli – sarcoidosis and orofacial granulomatosis

      - Foreign body giant cell containing lesions : foreign body granuloma

   B. Osteoclastic giant cell containing lesions

Various classifications has been proposed **[Table I]**,

Author	Basis of proposed classification
Chattopadhyay (1995) , Chatterjee et al (2015), Varghese and Prakash (2011)	Etiopathogenesis
Gupta et al (2014)	Origin
Chattopadhyay (1995)	Origin and etiology
Sankari et al (2014)	Functional characteristics
Mathew et al (2016)	Type of Giant cells
Haythron et al (1929), Quinn and Scheptkin (2009)	Arrangement, composition of organelles and function
Enneking and Campanacci (2016)	Radiographic appearance
Lucas (1976), Rosenberg et al (2001)	Pathology involved

Lesions with osteoclastic giant cells being the primary pathologic cells – Paget's disease

iii) Lesions with reactive osteoclastic giant cells formed secondarily by the activation of lesional stromal cells - Peripheral Giant Cell Granuloma (PGCG), Central Giant Cell Granuloma (CGCG), Cherubism, Aneurysmal Bone Cyst (ABC), Fibrous dysplasia, Brown tumor of hyperparathyroidism

iv) Touton giant cells Xanthoma, xanthogranuloma, fibroushistiocytoma.

v) Tumor giant cells [6] Tumors where giant cells are pathognomonic - Giant cell fibroma, Hodgkin's lymphoma, other anaplastic malignancies.

Cell Of Origin: [1,2]

Over the years a number of research has been done over the cell of origin of various giant cells and they are as follows:

1. Proliferating giant cells associated with tooth eruption (Geschicter and Copeland)
2. Endothelial cells
3. Proliferating mononuclear cells
4. Monocytes (Arnold Postlethwaite et al)
5. Mitotic/amitotic division & monocyte nuclei.

Formation Of Giant Cells:

Various theories of Giant cell formation[1,2] have been proposed

1. Multiple Nuclear Division Without Cytokinesis :

According to Harris[1,2,] nuclear division in a polykaryon is normally followed by the formation of a single mitotic spindle, leading to the production of a single hyperdiploid nuclei. He also stated that formation of giant cells (e.g. tumour giant cells) occurs by the nucleus of the dividing cell, while the body of the cell fails to divide. These giant cells are not derived from the macrophages but from the cells of the tumour either connective tissue or epithelial in nature. [7]

2. Macrophages Fusion:

Gorden and Cohen[1,2] in 1970 suggested that macrophages can fuse with other macrophages to form a giant cell in vivo. Three suggestions have been put forward to account for macrophage fusion in vivo.

i. Fusion Mediated by the Immune System

Macrophage polykaryons are commonly found in areas containing poorly removable foreign material. Frequently the foreign body is antigenic (fungi, tuberculosis, etc). Even when the foreign material itself has no antigenicity (e.g., glass) it is possible that inflammatory process itself produces antigens. It has been stated that immune system is probably responsible for macrophage fusion. It has been suggested phagocytosing macrophage fuse under the influence of lymphokines and the membrane changes associated phagocytosis may facilitate the adherence and fusion of macrophages initiating the formation of the giant cell.

ii. Fusion Resulting from the Recognition of an Abnormal Macrophage Surface by Young Macrophages.

Mariano and Spector showed that by enclosing a population of macrophages in diffusion chambers; in vitro giant cell formation was prevented. On leaving the chambers open, they found that the fresh in coming macrophages fused with those already inside the chamber to form giant cells. It was seen that being

enclosed within the chamber, the macrophages underwent mitosis, [8] which revealed many chromosomal abnormalities. These chromosomal abnormalities lead to the formation of an abnormal cell surface on aging population which is recognized by the fresh incoming cells leading to fusion. Contradicting Mariano and Spector's hypothesis later in the year 1977, Chambers[1,2] tested this hypothesis by exposing macrophages cultured in inflammatory exudates to fresh macrophages. It was observed that no fusion took place between two populations.

iii. Fusion as a result of Endocytic activity

Chambers[1,2] suggested that if the foreign material gets attached to the surface of the macrophages, it meets the phagosomic margins of the other cell. Attachment of any variety of substances (foreign material) to the macrophage surface is followed by formation of endosome margins, which then approach each other and fuse to complete the endosome formation. It was seen fusion occurred in between the margins of the two cells.

3. Formation of Giant Cells induced by Viruses:

Hernandez et al[1,2] suggested that fusion may be caused by large numbers of inactivated viruses or by much small infective virus. With the inactivated virus, the viral envelope attaches and leads to a reduction in the cell coat thickness. When the virus is in contact with more than one cell, it results in cell fusion. Antigens from the virus get incorporated into the polykaryon membrane, indicating that the fusion results from the viral envelope leading to a "bridge" between the two cells, which enlarges into complete cell fusion. The mechanism by which enveloped viruses enter cells has very well defined by Hernandez et al under molecular basis. It says binding and fusion of viruses with host cells is mediated by viral proteins and host cell surface molecules that are used as viral receptors.

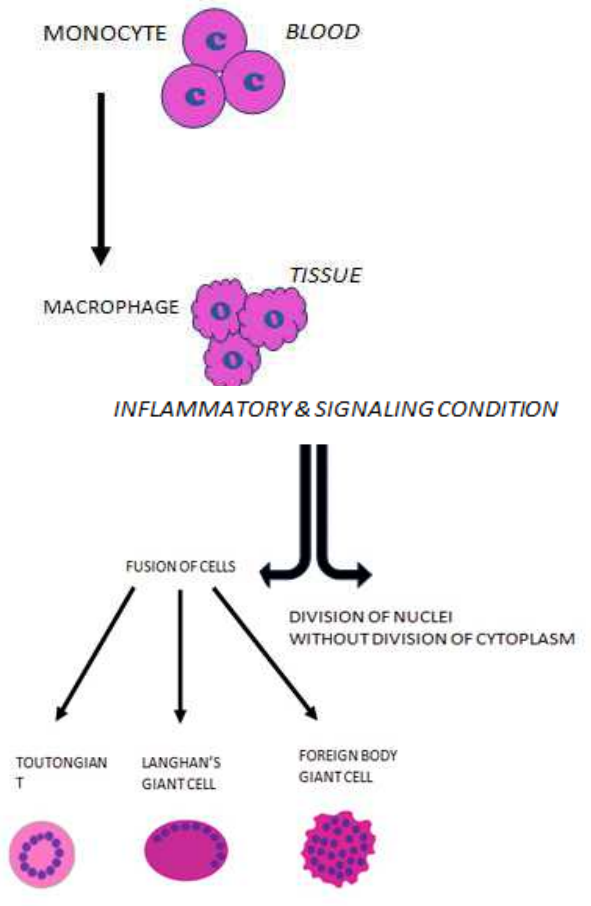
Molecular method of fusion:

For cells to undergo fusion a number of events need to occur sequentially to form a favourable environment for the same, the sequence of those events are as follows: 6

I. Induction of a Fusion-Competent Status
II. Chemotaxis
III. Cell–Cell attachment
IV. Cytoskeletal rearrangements
V. Fusion

Types of Giant Cells:

Multinucleated giant cells can be classified into several morphological variants **[Figure 1]**



Formation of multinucleated giant cells and its morphologic variants.

depending on the arrangement and composition of their organelles, as well as their functional characteristics.[7] Osteoclasts, odontoclasts, skeletal muscle fibers, syncytiotrophoblasts and megakaryocytes are the physiologically present multinucleated giant cells. Few of these also have a role to play in various pathological processes.[8]

Osteoclasts, as named by Kolliker[9] 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).[9] In addition a wide variety of factors like systemic hormones and growth factors influence the formation and function of osteoclasts. [10]

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[1]. The osteoclastic giant cells show positivity to cathepsin K, alkaline phosphatase, RANKL, osteoprotegerin & Cluster of Differentiation 68 (CD68).[9] 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 .

Odontoclasts are responsible for resorption of dental hard tissues in various physiological and pathological oral conditions. These cells are usually studied and compared with osteoclasts because of some overlapping morphological and biochemical characteristics. However, there are still some differences. Some studies had shown that, similar to osteoclastogenesis Receptor activator of nuclear factor K.B. (RANK), RANK-Ligand (RANKL) and Osteoprotegerin (OPG) are involved in odontoclastogenesis. Also, similar pathways [alphavbeta3 integrin pathway and c-Fms pathway] seem to operate during activation of both odontoclasts and osteoclasts. According to certain contradictory studies response of odontoclasts to parathyroid hormone extract and certain drugs was found to be different from that of osteoclasts. Thus, it can be proposed that there might be additional pathways involved in formation and activation of odontoclasts. Physiological root resorption is seen only during shedding of deciduous teeth. Whereas pathologic root resorption can be due to various causes like trauma as in orthodontic treatment, hormonal imbalance, various cysts and tumors affecting jaw bones and periodontal disease. Pathways for formation and activation of odontoclasts can vary slightly among these pathologies.[10]

Tumor giant cells :

Many epithelial and mesenchymal neoplasms contain tumor giant cells.[11] The nuclei of these giant cells are pleomorphic, often diploid, shows abnormal mitosis and resemble those of mononuclear tumor population. Tumor cells are known to possess an abnormal surface and are predisposed to fusion in different ways.[12] Many tumors have been shown to release extracellular enzymes 13 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. Josten M & Rudolph R12 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.[14]

Reed Sternberg Cells :

Reed–Sternberg cells (also known as lacunar histiocytes for certain types) are different giant cells found with light microscopy in biopsies from individuals with Hodgkin's lymphoma (also known as Hodgkin's disease; a type of lymphoma) primarily due to Epstein Barr Virus, and certain other disorders. They are usually derived from B lymphocytes. The Reed-Sternberg cell is typically binucleated ('owl eyenuclei'), although it may be multinucleated ("pennies on a plate"), with prominent nucleoli. Immunophenotypically, Reed - Sternberg cells are positive for CD15/CD30 and negative for CD45/CD20 both in nodal and extra nodal disease.[15]

Touton giant cells : [12]

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.[16] These Multinucleated giant cells (MGCs) are most frequently found in lesions containing cholesterol and lipid deposits, and are associated with various pathologic processes, such as xanthomas and xanthogranulomas.[17] Touton types of giant cells are appreciated in cases of fibrous histiocytoma.[18] The lipid droplets in the cytoplasm of these cells can be demonstrated in frozen section by special stains.[19] Lysozyme, α1 antitrypsin, CD68 & factor XIIIa can be used as a marker for differentiation of these multinucleated giant cells.[17]

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. Interferongamma (IF-γ) plays a central role in inducing Langhans' giant cell formation. These cells

show positivity to CD68.20 It has also been seen that larger the size and more the number of nuclei in MGCs, the virulence of disease increases. Lay et al21 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.[2113]

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.[9] FBGCs contain many nuclei (up to 100 - 200) that are arranged in a diffuse manner throughout the cytoplasm. 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.[9]

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 .[22,23]

Conclusion:

Inspite of recent advances in understanding the molecular and cellular basis of different types of giant cells formation and function, major challenges remain in appreciating the molecular and cellular similarities and differences of different giant cells. Continued research is essential, not only for its theoretical value, but also for its important potential clinical implications. Better knowledge of giant cells will both help to elucidate the pathology and diagnosis of various diseases, such as, central giant cell granuloma, fibrous dysplasia etc and also improve opportunities for therapeutic intervention.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Chatterjee A, Nazir H. Giant Cell Formation- A Review. IOSR-J Dent Med Sci. 2015;14(10): 98-101 .
2. Chambers TJ. Multinucleate giant cells. J Pathol. 1978;126(3):125-48.
3. Papadimitriou JM, Robertson TA, Walters NI. An analysis of the phagocytic potential of multinucleate foreign body giant cells. Am J Pathol. 1975;78(2):343-358.
4. Ranjan V, Chakrabarty S, Arora P, Rastogi T. Classifying giant cell lesions: A review. J Indian Acad Oral Med Radiol. 2018;30:297-301.
5. Mathew D G, Sreenivasan B S, Varghese S S, Sebastian J. Classification of giant cell lesions of the oral cavity: A fresh perspective. Oral Maxillofac Pathol J. 2016; 7(2): 710-716.
6. Gupta S, Kaur H, Gumber P, Fahmi N, Sharma K Gumber. A Giant cells in health and disease-a review. Int J Community Health and Med Res. 2016;2(2):60-65.
7. Ashish S, Vinay M, Sushmita S, Manisha N. Giant cells and giant cell lesions of oral cavity – A review. Cumhuriyet Dent J. 2014;17(2):192-204.
8. Ross MH Pawlina W. Histology. A text and atlas with correlated cell and molecular biology. 5th Edition ; Lippincott Williams & Wilkins.2006.
9. Brodbeck WG, Anderson J. Giant cell formation and function. Curr Opin Hematol. 2009;16:53-57.
10. Liu B, Yu SF, Li TJ. Multinucleated giant cells in various forms of giant cell containing lesions of the jaws express features of osteoclasts. J Oral Pathol Med. 2003;32(6):367-375.
11. Giant cells and giant cell lesions of oral cavity - a review. Shrestha A, Marla V, Shrestha S, Neupane M. Cumhuriyet Dent J. 2014;17(2):192-204.
12. Nicolson GL. Transmembrane control of the receptors on normal and tumor cells. Biochem Biophys Acta. 1976;457:57.

13. Weiss L. The cell periphery, metastasis and other contact phenomena. North Holland Pub Co, Amsterdam 1976;267-271.

14. Josten M, Rudolph R. Methods for the differentiation of giant cells in canine and feline neoplasias in paraffin sections. Zentralbl Veterinarmed A. 1997;44(3):159-166.

15. Gupta S, Kaur H, Gumber P, Fahmi N, Sharma K Gumber A. Giant cells in health and disease-a review. Int J Community Health and Med Res. 2016;2(2):60-65

16. Aterman K, Remmele, W, Smith M. Karl Touton and his 'xanthelasmatic giant cell.' A selective review of multinucleated giant cells. Am J Dermatopathol. 1988;10:257-269.

17. Consolaro A, Sant'Ana E, Lawall MA, Consolaro MF, Bacchi CE: Gingival juvenile xanthogranuloma in an adult patient: case report with immunohistochemical analysis and literature review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009;107:246-252.

18. Canelas MM, Cardoso JC, Andrade PF, Reis JP, Tellechea O. Fibrous Histiocytomas: histopathologic review of 95 cases. An Bras Dermatol. 2010;85(2):211-215.

19. Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ. Fitzpatrick's Dermatology in general medicine. 7th Edition. Vol 1 & 2. Mc Graw Hill. 2008.

20. Shafer, Hine, Levy. Shafer's Textbook of Oral pathology, 6th Edition; Elsevier: 2009.

21. Lay G, Poquet Y, Salek-Peyron P, Puissegur MP, Botanch C, Bon H et al. Langhans giant cells from M tuberculosis-induced human granulomas cannot mediate mycobacterial uptake. J Pathol. 2007;211:76-85.

22. Fortin JF, Barbeau B, Hedman H, Lundgren E, Tremblay MJ: Role of the leukocyte function antigen-1 conformational state in the process of human immunodeficiency virus type 1-mediated syncytium formation and virus infection. Virology. 1999;257:228-238.

23. Neville, Damm, Allen, Bouquot. Oral and Maxillofacial Pathology, 3rd Edition; Saunders: 2009.