Giant Cell: Cells Unite to Fight

Bhanu Priya[1], Vipul Jain[2], Aakanksha Malhotra[3]

ABSTRACT

Rokitansky and Langhans first reported multinucleated giant cells in tuberculous granulomas around a century ago. In process of tissue remodeling and repair the multinucleated giant cells (MGCs) acts as inextricable mediators. They also aid in removal of various pathogens and foreign materials (Vignery, 2005). Thus, for host survival they have a role in elimination of foreign substances, damaged tissue, and pathogens. Giant cells are supposed to arise from the monocyte precursors which forms subsequently to various mechanisms. These cells assume distinctly variable phenotypes depending upon the mechanism of their formation. This review focuses on the role of the giant cell in oral pathoses such as microbial lesions, cystic lesions, metabolic lesions and cancer.

Keywords: Multinucleated Giant Cells, Monocytes

INTRODUCTION

The term Giant cell is derived from a Latin word," giges; huge and cella; storeroom.[1] It is defined as an abnormally large tissue cell which often contains more than one nucleus and sometimes may appear as a merger of several normal cells. Multinucleated giant cells are broadly classified into physiologic and pathologic giant cells.[2] The physiologic giant cells are the osteoclasts present in bone, syncytiotrophoblast of the placenta and multinucleated cells of the skeletal muscle. Osteoclasts are large multinucleated cells which appear at or near the surface of bone resorption. When viewed under the light microscope, they may contain between 10 -100 nuclei in a section and are located in the Howship's lacunae on the bone surface. It originates from the mononuclear phagocyte precursors. Changes in the bone surface may lead to phagocytic recognition and in such instance, the bone becomes a "foreign body" and leads to the formation of foreign body giant cells, which are indistinguishable from osteoclasts in structure, function and origin.[3]

Syncytiotrophoblast which is a multinucleated continuous cell layer covering the surface of the placenta plays a vital role in the success of pregnancy. It has a protective role as the outermost component of the classical placental barrier between the mother and fetus. It helps in selective bi-directional transport of material between the maternal and fetal circulation and also synthesizes protein and steroid hormones.[4] Apart from this the occurrence of polykaryons elsewhere is considered to be pathologic.The pathologic giant cells are Langhans' giant cells, foreign body giant cells, inflammatory giant cells, tumor giant cells and Touton giant cells. There are also miscellaneous types of giant cells such as Aschoff cells of rheumatic nodule and Reed Sternberg cells of Hodgkin's lymphoma.[5]

CLASSIFICATION OF GIANT CELL LESIONS

The different classifications of giant cell lesions reflect advances in knowledge and changing concepts.

R.V. Subramanyam[6] (Table: 1)

Varghese. I and Prakash[5]

1. **Microbial lesions:** Tuberculosis, Leprosy, Actinomycosis, Sarcoidosis
2. **Tumour and tumour like lesions:** Central giant cell granuloma, Peripheral giant cell granuloma, Giant cell fibroma, Giant cell tumour, Osteosarcoma, Rhabdomyosarcoma, Hodgkin's lymphoma
3. **Cystic lesions:** Traumatic bone cyst, Aneurysmal bone cyst
4. **Metabolic lesions:** Hyperparathyroidism
5. **Osteodystrophic lesions**: Noonan-like multiple giant cell lesion syndrome
6. **Miscellaneous lesions**: Cherubism, Paget's disease, Fibrous dysplasia

FACTORS INVOLVED IN GIANT CELL FORMATION

Monocyte/macrophages are phagocytic leukocytes that play a multitude of functional roles in the body and represent as key players in both innate and acquired immunity. Fusion of macrophages can result in the formation of osteoclasts or a variety of different multinuclear giant cells (MGCs), each with unique properties and tissue distributions. 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.[2]

Macrophages, which have marked phagocytic activity, are large mononucleated cells which play an important role in the later stages of acute inflammation and some types of chronic inflammation. In instances when the individual macrophages are unable to deal with particles to be removed, they fuse together and form multinucleated giant cells. Examples of giant cell formation can be seen around a foreign body such as a fragment of bone, a piece of ligature, a crystal of

[1]PG Student, Department of Oral Pathology, Goa Dental College and Hospital, [2]Dental Officer, Dental Department of 356 Field Hospital, C/O 99 APO, [3]Junior Resident, Department of Psychiatry, India

Corresponding author: Dr. Bhanu Priya Senior Resident, Maulana Azad Institute of Dental Sciences, New Delhi-110002, India.

How to cite this article: Bhanu Priya, Vipul Jain, Aakanksha Malhotra. Giant cell: cells unite to fight. International Journal of Contemporary Medical Research 2019;6(7):G9-G13.

DOI: http://dx.doi.org/10.21276/ijcmr.2019.6.7.28

Infections	Non-infective granulomas	Non-neoplastic lesions	Cysts	Neoplasms	Miscellaneous
Bacterial Tuberculosis Syphilis Leprosy Actinomycosis Yaws Bejel Rhinosarcoma Osteomyelitis	Wegener's granulomatosis Midline lethal granuloma Sarcoidosis Plasma cell granuloma	***Soft tissue*** Peripheral giant cell granuloma Giant cell fibroma Pseudosarcomatous fasciitis Xanthogranuloma Traumatic granuloma	Aneurysmal Bone cyst Calcifying odontogenic cyst Solitary bone cyst	***Benign*** Giant cell tumour Osteoid osteoma Osteoblastoma Central Haemangioma	Internal resorption External resorption Massive osteolysis Spindle and/or epitheliod cell nevus
Viral Herpes simplex Herpes zoster Mumps CMV infection Measles ***Fungal*** Histoplasmosis Blastomycosis Sporotrichosis Coccidiodomycosis Other deep fungal infections ***Protozoal*** Leishmaniasis ***Chlamydial*** Lymphogranulomavenerum		***Bone*** Central giant cell granuloma Brown tumour of hyperparathyroidism Cherubism Fibrous dysplasia Paget's disease Histiocytosis X/ LCD Osteomalacia		***Malignant*** Osteosarcoma Hodgkin's Lymphoma – Reed-Sternberg cells Reticular cell sarcoma Lymphosarcoma Other malignant tumours with tumour giant cells	

Table-1: Classification of giant cell lesion by R.V. Subramanyam.[6]

Volume 6 | Issue 7 | July 2019 | ICV: 98.46 | International Journal of Contemporary Medical Research ISSN (Online): 2393-915X; (Print): 2454-7379

Contributing Factor	Osteoclasts	Foreign Body Giant Cells
Fusion (Adhesion) Substrate	Bone, Dentin	Implanted biomaterials Hydrophobic/hydrophilic Neutral/Ionic
Surface (Adsorbed) Proteins	Osteopontin Vitronectin Fibrin(ogen) Bone sialoprotein	Complement component (iC3b) Vitronectin Fibrin(ogen)
Adhesion Receptors,Integrins	αVβ3	
CD47	α5β1, α3β1	AMβ2, αXβ2
Soluble Fusion Mediator	CCL-2 RANKL M-CSF TNF-α IL-1	CCL-2 IL-4 IL-13 INF-γ IL-3 Con A PHA
Cell Surface Fusion Mediators (Receptors/Ligands	DC-STAMP	DC-STAMP
CD48	Mannose receptor (CD26) Avβ3 RANKL E-Cadherin CD44, CD81, CD9 Connexin 43 P2X7 receptor Presenilin 2	CD13 (aminopeptidase-N) Galectin-3 E-Cadherin CD44, CD81, CD9 Connexin 43
Phenotypic Expression	Cathepsin K Acid	Phagocytosis (frustrated) Acid Reactive oxygen intermediates lymphocyte co-stimulators (CD98, CD44)

CCL-2: Chemokine (C-C motif) ligand 2, RANKL: Receptor activator of nuclear factor kappa-B ligand, M-CSF: Macrophage colony-stimulating factor, TNFα: Tumor necrosis factor alpha, P2X7 receptor: Purinergic receptor P2X- ligand gated ion channel-7, ConA: Concanavalin A, PHA: Phytohaemagglutinin, DC-STAMP: Dendritic cell-specific transmembrane protein

Table-2: Factors Contributing to the Adhesion and Fusion of Monocytes/Macrophages in the Formation of Giant Cells.[7]

cholesterol or even a splinter of wood. For this reason the cells are called foreign body giant cells. (Table: 2)

FORMATION OF GIANT CELL

The two theories that were considered for giant cell formation are:[2]

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

Doan, Sabin and Forkner (1930) on the basis of experiments on the blood and tissues of rabbits using different substances found that two types of giant cells were produced as a response to foreign substances. The first type contained a central rosette surrounded by nuclei in the periphery which is considered to be the epitheliod or Langhans giant cell which was formed due to nuclear division. Second group of cells with irregular arrangement of nuclei were considered to be foreignbody type giant cells and thought to arise due to fusion of monocytes.[8] Van Furth (1972) proposed that the MGC in granulomas are formed by fusion of macrophages rather than by division and non-disjunction of cells. Which was showed by radio-labeling studies on lymph nodes of sarcoidosis. Forkner suggested that both mechanisms were involved in giant cell formation. He attributed the difference of opinion to be due to failure of recognition of both these types of cells i.e. due to division or non-disjunction.

Some auto-radiographic studies also revealed that giant cells indeed form due to fusion, which has been supported by other authors also.[9,10]

The cell fusion results from alteration of cell surface followed by plasma membrane approximation and establishment of continuity between the apposed lipid bilayers.

The process of fusion can occur by three mechanisms:

1. An immune mediated phenomenon production of large amount of lymphokines response to antigenic material and in case of non-antigenic foreign material inflammatory process itself produces antigen which is responsible for macrophage fusion.[11]
2. By cell fusion of "young macrophages" and "old cell" with altered and abnormal cell surface.[12]
3. By simultaneous attempt of two or more macrophages to ingest foreign particles.[13]

Osteoclasts

The hormonal alteration and physical stresses lead to alteration in physicochemical properties of bone which start acting as foreign body. This altered bone is recognized by macrophages for phagocytosis and macrophages accumulated on bone surface. These macrophages fuse to form osteoclast, which contribute in bone homeostasis and remodeling. Their precursors derived from bone marrow as early mononuclear macrophages, circulate in blood,

and bind to the surface of bone. While the mechanism of recognition and target binding present on bone's surface is unknown, the integrin αvβ3 is the dominant osteoclast integrin and the marker of the osteoclast phenotype, which is initially absent on macrophage precursors, but progressively induced by RANKL. The αvβ3 integrin recognizes the RGD (Arg-Gly-Asp) tripeptide sequence in several extracellular matrix macromolecules such as osteopontin, fibronectin, vitronectin, and fibrinogen.

Osteoclast formation is driven mainly by two cytokines, RANKL and M-CSF. RANKL is a member of the TNF superfamily and is considered the essential osteoclastogenic cytokine and is also expressed on osteoblasts. Cell surface RANKL interacts with its receptor, RANK, on osteoclast progenitors. Osteoprotegerin (OPG) is another member of the TNF superfamily is also synthesized by osteoblasts and their precursors. OPG recognizes RANKL and can thus function as a decoy receptor, competing with RANK. Overproduction of RANKL can lead to osteoporosis whereas overproduction of OPG can lead to osteopetrosis.[7,14]

Yagi and co-workers studied a knock-out mouse model and revealed that dendritic cell-specific transmembrane protein (DC-STAMP) as being required for the fusion of both osteoclasts and foreign body giant cells.[7]

Foreign body giant cell

The inflammatory giant cell appears regularly in response to a wide variety of stimuli and is commonly seen. Many types of tissues and tumors infected with certain viruses also exhibit the presence of polykaryons. These multinucleate cells regularly appear as part of the response to the presence in tissues of a variety of foreign or insoluble substances like deposition or implantation of poorly soluble sterile materials in the tissues, infective granulomas and granulomatous diseases of unknown etiology.

In an in vitro study of human granuloma model the role of mycobacterial envelope glycolipids in granuloma formation was revealed.[13] In this model, it was also seen that the proinflammatory glycolipids induce the fusion of granuloma macrophages into multinucleated giant cells and this process occurs through a Toll-Like Receptor 2-dependent, ADAM metallopeptidase domain 9 (ADAM9)- and β1 integrin mediated pathway.[7]

However, it generally accepted that FBGC are generated by macrophage fusion and serve the same purpose as osteoclasts, degradation/resorption of the resorption of the underlying substrate.[7] Unlike osteoclasts, which adhere to bone, FBGC 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.

The β1 and β2 integrin receptor families have been identified as necessary and sufficient mediators of adhesion during monocyte-to-macrophage development and IL-4-induced FBGC formation.[7,16]

Neoplastic giant cell

Tumor giant cells are large cells and have one or several nuclei which are not very numerous. They are formed by the nucleus of the cell dividing, while the body of the cell fails to divide. These cells are not derived from the macrophages but from the cells of the tumor, whether connective tissue or epithelial in nature. The nuclei of the giant cells resemble those of the mononuclear tumor population. The nuclei are pleomorphic, often hyperdiploid and often show abnormal mitoses.[3]

During initial tumor formation, mononuclear histiocytic cells are recruited to the site of the tumor, and fuse to form MGCs. Receptor activator of nuclear factor κB ligand (RANKL) is expressed by neoplastic giant cell tumor stromal cells, promoting fusion with macrophage colony stimulating factor (M-CSF) acting as a cofactor. Neoplastic giant cells are formed by heterogeneous cell fusion, endomitosis/neosis, ectopic induction of meiosis-like processes, drug induced depolymerization or hyperpolymerization of microtubules and cellular cannibalism.

DISCUSSION

Giant cells are commonly encountered in various lesions of the oral cavity. The presence of these giant cells and their appearance sometimes give a clue for the diagnosis and prognosis. In case of high virulence Langhans type giant cell contains more than 15 nuclei per cell whereas, low virulence Mycobacterium infection (M. avium and M. smegmatis) shows less than seven nuclei per cell.[7]

Giant cells containing up to 20-50 nuclei are associated with inflammatory conditions, whereas, more than 50 nuclei are associated with neoplasms.[15] So far a number of studies were done to understand their role and to correlate their presence with specific lesions. The term giant cell lesion covers nosologic entities.

When the individual cells are not able to contain pathogens, they unite and form multinucleated giant cells to attack extracellular material, such as larger pathogens and foreign material. Thus, their role in elimination of foreign substances, damaged tissue, and pathogens is essential to host survival and prevention of spread of infection.

CONCLUSIONS

Multinucleated giant cells provide a vital clue to the diagnosis. Various theories have been put forward to explain their genesis. Although, the fusion theory is most accepted theory for formation of multinucleated giant cells, the exact mechanism still remains to be understood. Whereas, the clinician and researchers for proper diagnosis and management required a definite criterion to identify individual giant cells in any giant cell lesions.

List of abbreviations

MGCs: Multinucleated giant cells; CMV infection: Cytomegalovirus infection; LCD: Langerhans cell disease; CCL-2: Chemokine (C-C motif) ligand 2; RANKL: Receptor activator of nuclear factor kappa-B ligand; M-CSF: Macrophage colony-stimulating factor; TNFα: Tumor necrosis factor alpha; P2X7 receptor: Purinergic receptor P2X- ligand gated ion channel-7; ConA: Concanavalin

A; PHA: Phytohaemagglutinin; DC-STAMP: Dendritic cell-specific transmembrane protein; ADAM9: ADAM metallopeptidase domain 9; FBGC: Foreign body giant cells; IL-4: Interleukin-4.

AVAILAIBILITY OF DATA AND MATERIALS

An extensive search of medical and dental databases using engines like PubMed, Cochrane, Research gate was done to gather the knowledge for this review. “Multinucleated giant cell”, “Foreign body giant cell” and “ Macrophage fusion markers” were the main keywords utilised in scrutinizing the online database. Studies till 2018 were included in the review.

REFERENCES

1. David P. Clark, Molecular Biology: academic cell update edition. London: Elsevier, 2010.
2. Postlethwaite A E, Jackson B K, Beachey E H, Kang A H, Formation of multinucleated giant cells from human monocyte precursors. Journal of experimental medicine, 1982; 155:168-178.
3. Chambers T J, Multinucleate giant cells. J Path 1978; 126:125-148.
4. Paul S, Gupta PD, Jailkhani BL, Talwar GP,Resistance of human syncytiotrophoblast to hypotonic and thermal stress. Journal of Reproduction and Fertility, 1980, 58:183-187.
5. Ipe Varghese, Ashwin Prakash, Giant cell lesions of oral cavity. Journal of Oral & Maxillofacial Pathology, 2011; 2:107-110.
6. R.V. Subramanyam Classification of Giant cell lesions.
7. William G. Brodbeck and James M. Anderson, Giant cell formation and function. Current Opinion in Hematology, 2009;16: 53–57.
8. Claude E. Forkner, The origin and fate of two types of multi- nucleated giant cells in the circulating blood.The Journal of Experimental Medicine, 1930;52:279-299.
9. Mark T. Quinn and Igor A. Schepetkin, Role of NADPH oxidase in formation and function of multinucleated giant cells.Journal of Innate Immunity. 2009;1:509–526.
10. T. C. M. Th. Van Maarsseveen, W. Vos and P. J. van Diest, Giant cell formation in sarcoidosis: cell fusion or proliferation with non-division?Clinical and Experimental Immunology, 155: 476–486.
11. Mariano M, Spector WG, The formation and properties of macrophage polykaryons (inflammatory giant cells).J Pathol. 1974;113:1-19.
12. Willoughby DA, Ryan GB, Evidence for a possible endogenous antigen in chronic inflammation.J Pathol. 1970;101:233-9.
13. Geraint T Williams, W Jones William, Granulomatous inflammation- a review.J ClinPathol, 1983;36:723-733.
14. Soysa NS, Alles N, Aoki K, Ohya K, Osteoclast formation and differentiation: an overview.Journal of Medical and Dental Sciences. 2012;59:65-74.
15. RostyslavHorbay, RostyslavStoika,Giant cell formation: the way to cell death or cell survival?Central European Journal of Biology. 2011;6:675-684.
16. Amy K. McNally and James M. Anderson, ß1 and ß 2 integrins mediate adhesion during macrophage fusion and multinucleated foreign body giant cell formation. American Journal of Pathology, 2002;160:621-630.

Source of Support: Nil; **Conflict of Interest:** None

Submitted: 06-06-2019; **Accepted:** 28-06-2019; **Published:** 25-07-2019