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Compendium on Giant cells – A unique review consolidating concepts of formation and associated lesions

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Abstract

Giant cell formation forms an important concept in understanding etiopathogenesis of various oral pathologies. Till date numerous concepts have been proposed to elucidate their pathogenesis. However, a consensus is yet to be developed. In the quest to explore all the possible theories related to their formation, the authors realized that till date there is no single literature piece explaining the concepts. Also, the theories have been published in very old papers which are difficult to access by the students interested in learning more about the topic. Hence this compendium is an effort by the authors to simplify the access and explanation of this topic for the students and other researchers.

Keywords: Giant cell, syncytium, Polykaryocytes

Introduction

A giant cell is a mass formed by the unification of multiple individual cells (usually macrophages) which go through specific intercellular interactions leading to the formation of a multinucleated cell with a single cytoplasmic compartment.[1] These cells are unusually large or gigantic, inflammatory, are often phagocytic and are also called as multinucleated giant cells (MNGCs), polykaryocytes or syncytium. MNGCs are often seen at the sites of chronic inflammation or granulomatous inflammation. They were first seen by Rokitansky and Langhans in 1868 in a case of tuberculous granuloma.[1] Broadly the MNGCs can be classified into 3 types - osteoclasts, foreign body giant cells (FBGCs), and Langhans giant cells.[2] While Osteoclasts would be commonly found functioning as bone resorbing cells under physiological conditions in bone, the FBGCs and Langhans types are formed during inflammatory reactions like granulomas or against foreign material like implants and protheses.[3,4]

Numerous head and neck pathologies with diverse etiopathogenesis exhibit MNGCs e.g., Tuberculosis, Leprosy, Giant cell granulomas, Giant cell tumor, Hyperparathyroidism, Calcifying odontogenic cyst etc. Although, MNGCs have diagnostic importance, yet it is surprizing that there is very less clarity and no consensus about their origin and role based on the immunohistological, ultrastructural and enzymatic studies. Although it has been almost 150 years of knowing about this entity, yet there is dearth of literature discussing the concepts related to their formation. A few authors have tried to consolidate the phenotype, biologic activities and mechanism of formation.[5,6]

Hence, this paper is an attempt to enlighten the readers about these enigmatic cells, their appearance, origin, formation and lesions associated with them.

Formation of Giant Cells

Till date numerous hypothesis have been proposed to explain the formation of MNGCs, however, there is still no consensus regarding the pathogenesis. The following concepts have been put forth by various authors:

1. Historical Concepts

Harris showed that after a polykaryon undergoes nuclear division a single mitotic spindle is formed, which creates a single hyperdiploid nucleus.[7] Borrel (1893) was the first to suggest that MNGCs are fused masses of mononuclear leucocytes.[8]

2. Fusion of Cell Membranes

According to this concept, all mammalian cells carry an overall negative charge on their surface.[9] The thickness of surface coat of cells is reduced due to

some unknown agent which brings the negatively charged surfaces closer and causes an electrostatic displacement of intramembranous calcium.[10] It is a known fact that Calcium is important in maintaining membrane stability, and the destabilisation may be the cause of membrane fusion.[11]

3. Induction by Viruses

The attachment of viral envelope to the host cell surface leads to a decrease in cell coat thickness. Hence the viral envelope fuses with the cell membranes of two adjacent cells. Forming a "bridge" between them, leading to formation of a giant cell e.g., Warthin – Finkeldey giant cells in measles.[12] (Figure 1)

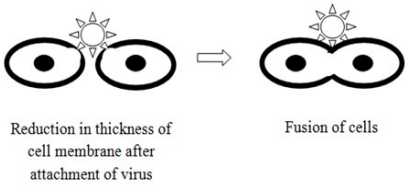

Figure 1: Formation of Warthin – Finkeldey giant cells

4. Role of Macrophages

Mariano and Spector presented that when certain macrophages were enclosed in the chamber, they undertook mitosis thereby revealing many chromosomal abnormalities. When the chambers were left open, the fresh incoming macrophages fused with those already inside the chamber to form giant cells. They suggested that chromosome abnormalities lead to the formation of an abnormal cell surface on the ageing population which is recognized by fresh incoming cells and leads to their fusion.[13,14] (Figure 2)

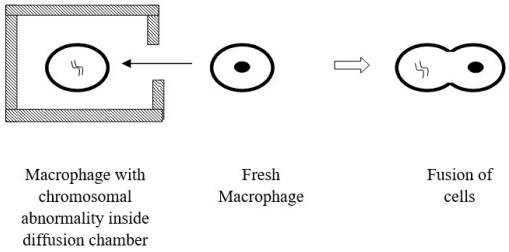

Figure 2: Role of macrophages in giant cell formation

5. Induction by Endocytic Activity

Chambers (1977) proposed that if a material is attached to the surface of two macrophages, each macrophage would form endosome margins. The endosomic margins of both macrophages then meet each other resulting in cell fusion.[15-18] (Figure 3)

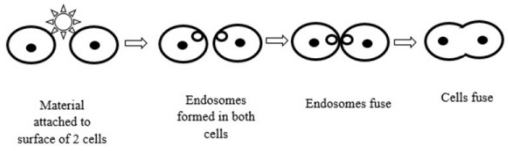

Figure 3: Giant cell formation by Endocytic activity

6. Induction by Foreign Body

Foreign body giant cells (FBGC) are commonly found in areas where it is difficult to remove foreign material and where the size of foreign particle is too large to permit macrophage phagocytosis. Usually, it is the foreign material which possesses antigenic properties (fungi, tubercle bacilli etc) but it is even possible that the inflammatory process itself produces antigens.[19] Various authors have stated that the β1 and β2 integrin receptor families are necessary mediators in formation of this variety of giant cells.

7. Induction by Bacteria ie, Mycobacterium

Some authors have even proposed that the number of nuclei within a giant cell can be correlated with the virulence of mycobacterium leading to their formation. For example, a high virulence mycobacterium like M. tuberculosis induces formation of large multinucleated giant cells with more than 15 nuclei per cell; whereas low virulence mycobacterium species, e.g., M. avium and M. smegmatis produce giant cells with low numbers of nuclei (less than 7) per cell. [20-21]

A summary of various proposed mechanisms of giant cell formation has been presented in Figure 4.

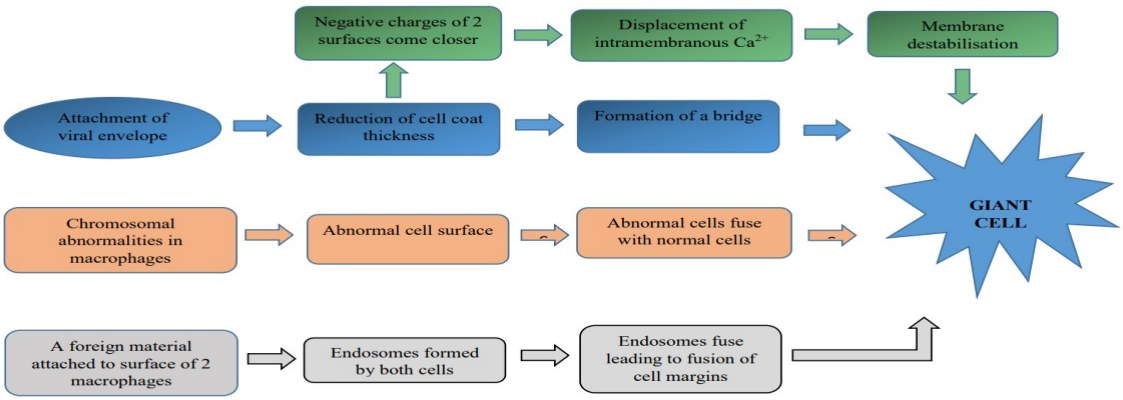

Figure 4: Summary of various concepts of giant cell formation

Giant Cell Lesions

The lesions associated with giant cells can be broadly categorised as Infections (Bacterial, Viral, Fungal and Granulomatous), cysts, Non neoplastic soft tissue or bony lesions, benign or malignant neoplasms or miscellaneous lesions. In this section we will discuss some of the common lesions associated with giant cells. **(Table 1)**

Table 1: Various lesions associated with giant cells

	Lesion	Speculated origin of giant cell	Type of giant cell
Bacterial infections	Tuberculosis	Macrophage	Langhans/ Foreign body
	Syphilis	Macrophage	Foreign body
	Leprosy	Macrophage	Langhans/ Foreign body
Viral infections	Herpes simplex	Epidermal cell	MNGCs with "ground glass nuclei"
	Herpes zoster	Epidermal cell	Tadpole or tear drop shaped giant cells.
	CMV infection	Epithelial/ Endothelial cells	Nothing specified
	Measles	Follicular dendritic cells	Warthin Finkeldey
Fungal infections	Sporotrichosis		Langhans
	Histoplasmosis		Langhans
	Coccidiomycosis	Macrophage	Nothing specified
Granulomatous Infections	Sarcoidosis	Macrophage	Langhans/Foreign body/Touton
	Wegener's granulomatosis	Macrophage	Langhans/ Foreign body
	Periapical granuloma	Macrophage	Foreign body/ Touton
	Foreign body reaction	Macrophage	Foreign body
Cysts	Aneurysmal bone cyst	Osteoclast	Osteoclast-type
	COC		Foreign body
	Traumatic bone cyst	Osteoclast	Osteoclast like
Non neoplastic soft tissue lesions	PGCG	Osteoclast/Histiocyte /phagocytic response	MNGCs with several dozen vesicular or pyknotic nuclei
	Giant cell fibroma	Fibroblast	Stellate shaped MNGCs
	Pseudosarcomatous fascitis	Osteoclast/Foreign body	Osteoclast like/ Foreign body type

	Xanthogranuloma	-	Touton
	Traumatic granuloma	Macrophage	Nothing specified
Non neoplastic bony lesions	CGCG	Osteoclast	Foreign body
	Brown tumor	Osteoclast	Osteoclast like
	Cherubism	Osteoclast	Osteoclast like
	Fibrous dysplasia	Macrophage	Nothing specified
	Paget's disease	Osteoclast	Osteoclast like
	Histiocytosis X	Histiocyte	Histiocytic giant cells
Benign neoplasms	GCT	Osteoclast/mononuclear cells	Osteoclast like
	Osteoid osteoma	Osteoclast	Osteoclast like
	Osteoblastoma	Osteoclast	Osteoclast like
Malignant neoplasms	Hodgkins lymphoma	B cells/ T cells	Reed Sternberg
	Osteosarcoma	Tumor cells/osteoclast	Osteoclast like
Miscellaneous lesions	Internal resorption	Osteoclast	Osteoclast like
	External resorption	Osteoclast	Osteoclast like
	Spindle and/or epitheloid cell naevus	-	Foreign body

Tuberculosis

The histologic lesion of TB shows a granulomatous inflammatory reaction composed of granulomas showing central caseous necrosis. *M. tuberculosis* provokes a characteristic macrophage response in which focal zones of macrophages become surrounded by a of lymphocytes and fibroblasts.[10] Fusion of macrophages results in the formation of Langhans giant cells nuclei distributed around the periphery of the cytoplasm in horse-shoe fashion/ arrangement. Some authors have also quoted that interactions with CD40 and its ligand (CD40L) as well as interefron gamma lead to the formation of Langhans' giant cells.[21]

Sarcoidosis

It has been proposed that in sarcoidosis, the giant cells mostly are of a monocyte – macrophage lineage. The types usually seen are Langhans-type with an arcuate arrangement of nuclei and a Foreign-body type with random arrangement of nuclei. In rare instances, Touton-like giant cells have been also reported in subcutaneous sarcoidosis.[22] The touton variety is known to have a central homogeneous cytoplasm surrounded by a ring of nuclei. The nuclei are surrounded by foamy cytoplasm. The theory proposed for formation of giant cells states that they are formed because of the fusion of the epithelioid mononuclear cells. They may also be seen sometimes with inclusion bodies such as Schaumann bodies or stellate asteroid bodies.[23]

Measles

The giant cells in measles are formed in the prodromal or pre-eruptive period of the disease and are known as Warthin-Finkeldey giant cells.24 As described by Warthin, these giant cells cells are round or irregularly lobed and have nuclei arranged in a grape-like cluster in the center of the cell. There were some with as many as 70 to 100 nuclei.[25] Warthin proposed that it was a "defence cell" formed by "amitotic division of nuclei in hyperchromatic cells resembling lymphocytes."[26] Finkeldey suggested that "while one can assume that there is an excessive nuclear proliferation following an abnormal stimulus, one can also find pictures that lead one to think of cell-fusion."[26] Mayerhofer seconds the suggestion of an allergic phenomenon.[27]

Peripheral giant cell granuloma (PGCG)

The classic histologic picture of PGCG shows numerous giant cells lying within the stroma consisting of fibroblasts, immature cells and ground substance. [28] Numerous hypotheses have been proposed for their formation. Certain researchers have proposed that the giant cells are a a phagocytic response to haemorrhage within the granulation tissue.[29] While authors propose that giant cells originate either from osteoclasts or mononuclear histiocytes. Research conducted by Flangan *et al* provided evidence that the giant cells resemble osteoclasts. They used giant cells excavated from bone *in-vitro* for their research.[30]

Central giant cell granuloma (CGCG)

The histopathologic picture of CGCG is characterized by the numerous MNGCs embedded in a fibrocellular stroma usually found closer to blood vessel walls.[31] Although the exact variety of giant cells seen is still uncertain, but most likely they are phagocytes, foreign body cells, or osteoclasts. [19] Several theories have been proposed for the presence of the giant cells. Some authors have proposed that the tumor fibroblasts lead to accumulation of monocytes and later transform them into MNGCs.[32] While some others like Jaffe (1953), and Bernier and Cahn (1954) suggested that the giant cells are formed as a phagocytic response to haemorrhage in the chronic reparative granulation tissue. Mallory (1911) suggested that MNGCs arise from macrophages.[33]

Giant cell tumor (GCT)

GCT of bone is a distinctive neoplasm of undifferentiated cells. It has been proposed that MNGCs are the outcome of fusion of the proliferating mononuclear cells.[34] The giant cells are usually large and have over 20 or 30 nuclei, most of them arranged toward the center. They resemble osteoclasts at all levels: morphologic, ultrastructural determined primarily by expression of CD68 (ruffled border and abundant mitochondria) enzyme histochemical (abundant tartrate-resistant acid phosphatase, cathepsin K, lysozyme, α1-antitrypsin, α1-antichymotrypsin and other hydrolytic enzymes), and immunohistochemical (positivity for microphthalmia-associated transcription factor (Mitf), and other histiocytic markers). Due to these similarities, GCT of bone is also known as osteoclastoma. [34]

Hodgkins Lymphoma (HL)

The giant cells of Hodgkins lymphoma are known as Reed-Sternberg cells. Activation of the transcription factor NF-κB (Nuclear factor kappa beta) either by EBV (Epstein Barr Virus) infection or by some other mechanism is a common event in classical HL. It is hypothesized that activation of NF-κB saves the "crippled" germinal-center B cells which are unable to express Immunoglobulins from apoptosis. This further leads to other unknown mutations that work in partnership to produce Reed Sternberg cells.[35] Reed–Sternberg cell is a large cell (20–50 μm in diameter or more) with abundant weakly acidophilic or amphophilic cytoplasm, which may appear homogeneous or granular. The nucleus is bilobed or polylobed so that the cell appears binucleated or multinucleated and is usually vesicular but with some coarse chromatin clumps scattered throughout with a thick, sharply defined nuclear membrane. In the most typical example of the Reed–Sternberg cell, the two nuclear lobes face each other ('mirror image'), resulting in the 'owl eye' appearance. When multilobation occurs, the appearance has been likened to that of an 'egg basket'.[36]

Internal Resorption

Vascular changes occurring during the process of internal resorption attract numerous macrophages which eventually differentiate into osteoclasts ie MNGCs.[37] MNGCs are also described in lacunae of hard tissue next to polymorphonuclear neutrophils. Some researchers have also observed numerous multinucleated dentinoclasts adjacent to the dentinal wall which are histologically and functionally identical to osteoclasts.[38]

Foreign Body Reaction

Foreign body reaction is the end-stage response of the inflammatory and wound healing responses which occur after implantation of a medical device, prosthesis, or biomaterial. It is a defence mechanism to eliminate endogenous and exogenous foreign material and is different in soft tissue and hard tissue. It is usually composed of macrophages and giant cells. MNGCs are frequently of foreign body type, with nuclei scattered irregularly throughout the cytoplasm, but Langhans giant cells can also be seen.[39]

Calcifying Odontogenic Cyst (COC)

COC is known for the presence of ghost cells in its epithelial lining. It has been proposed that when the ghost cells encounter the connective tissue wall of the cyst, they may induce a foreign body reaction leading to the formation of MNGCs. [40]

Conclusion

Extensive literature research of head and neck pathologies containing giant cells could not bring forth the exact etiopathogenesis and prognosis of these mysterious cells. Although the researchers have even tried to synthesize the giant cells "in-vitro" but have not succeeded. In some of the giant cell lesions, the pathogenesis/ origin is well evident but in majority of them, it still remains questionable.

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Conflict of Interest

None to declare

References

1. Postlethwaite AE, Jackson BK, Beachey EH, Kang AH. Formation of multinucleated giant cells from human monocyte precursors. J of Exp Med. 1982; 155:168-78.
2. Anderson JM. Multinucleated Giant Cells. Med. Oral. 2000; 7, 40–47. Doi: 10.1097/00062752-200001000-00008.
3. Drissi H, Sanjay A. The Multifaceted Osteoclast; Far and beyond Bone Resorption. J. Cel. Biochem. 2016; 117, 1753–1756. doi:10.1002/jcb.25560
4. Wang H, Jiang H, Teles RMB, Chen Y, Wu A, Lu J, et al. Cellular, Molecular, and Immunological Characteristics of Langhans Multinucleated Giant Cells Programmed by IL-15. J. Invest. Dermatol. 2020; 140, 1824–1836. e7. doi:10.1016/j.jid.2020.01.026
5. Ahmadzadeh K, Vanoppen M, Rose CD, Matthys P, Wouters CH. Multinucleated Giant Cells: Current Insights in Phenotype, Biological Activities, and Mechanism of Formation. Front Cell Dev Biol. 2022 Apr 11; 10:873226. doi: 10.3389/fcell.2022.873226. PMID: 35478968; PMCID: PMC9035892.
6. Akinyamoju AO, Soyele OO, Saiki TE, Adesina OM. Giant Cell Lesions of the Jaws: A Review and Comparative Histopathological Study. West Afr J Med. 2020 Jan-Mar; 37(1):26-31. PMID: 32030708.
7. Harris H.1968. In Nucleus and cytoplasm, Clarendon Press, Oxford.
8. Borrel A. Tuberculose pulmonaire experimentale. Annals Inst. Pasteur. 1893; 7:593.
9. Weiss L, Woodbridge RF. Some biophysical aspects of cell contacts. Fed. Proc. 1967; 26:88.
10. Poste G, Allison AC. Membrane fusion reaction: A theory. J Theoret Biol. 1971; 32:165.
11. Weiss L. 1967.The cell periphery, metastasis and other contact phenomena. North-Holland, Amsterdam.
12. Heinej W, Schnaitman CA. Entry of vesicular stomatitis virus into L-cells. J Vivol. 1971; 8:786.
13. Mariano M, Spector WG. The formation and properties of macrophage polykaryons (inflammatory giant cells). J Pathol. 1974; 1:113.
14. Pereira, M., Petretto, E., Gordon, S., Bassett, J. H. D., Williams, G. R., and Behmoaras, J. Common Signalling Pathways in Macrophage and Osteoclast Multinucleation. J. Cel Sci. 2018; 131, jcs216267. doi:10.1242/jcs.216267
15. Chambers TJ. Fusion of macrophages following simultaneous attempted phagocytosis of glutaraldehyde-fixed red cells. J Pathol.1977; 122:71.
16. Chambers TJ. The mechanism of fusion of hamster macrophages induced by antimacrophage serum. J Pathol.1977; 122:163.
17. Chambers TJ. Fusion of hamster macrophages induced by lectins. J Pathol. 1977; 123:53.
18. Chambers TJ. Studies on the phagocytic capacity of macrophage polykaryons. J Pathol. 1977; 123:000.
19. Brodbeck WG, Anderson JM. Giant cell formation and function. Curr Opin Hematol. 2009; 16(1):53-7.
20. illiams JW, Erasmus DA, Jenkins D, James EM, Davies T. A comparative study of the ultrastructure and histochemistry of sarcoid and tuberculous granulomas. Fifth International Conference on Sarcoidosis. Edited by L Levinsky, F Macholda. Prague, Universita Karlova Praha. 1971:115-120.
21. Sakai H, Okafuji I, Nishikomori R, Abe J, Izawa K, Kambe N, et al. The CD40-CD40L axis and IFN-γ play critical roles in Langhans giant cell formation. Int Immunol.2012; 24:5–15.
22. Weedon D. Weedon's skin pathology. 3rd ed. London: Churchill Livingstone; 2010.
23. Suresh L, Radfar L. Oral sarcoidosis: a review of literature. Oral Diseases. 2005; 11:138-45.
24. Bunting CH. The giant-cells of measles. Yale J Biol Med. 1950; 22(6):513–9.
25. Warthin AS. Occurrence of numerous large giant cells in the tonsils and pharyngeal mucosa in the prodromal stage of measles. Arch Path Chic. 1931; 11:864.
26. Finkeldey, W. Uber Riesenzellbefunde in den Gaumenmandel, us. Virchows Arch.1931:281-323.
27. Mayerhofer E. Die prodromale Masernangina. Zschr. Kinderh.1934; 56:42.
28. Carvalho YR, Loyola AM, Gomez RS, Araujo VC. Peripheral giant cell granuloma-An immunohistochemical and ultrastructural study. Oral Diseases. 1995; 1:20-5.
29. Jaffe HL. Giant cell reparative granuloma traumatic bone cyst and fibrous (fibro-osseous) dysplasia of the jawbones. J oral surgery. 1953:6; 159-75.
30. Flanagan IS, Tinkier SMB, Horton MA. Williams DM. Chambers TJ. The multinucleate cells in giant cell granulomas of the Jaw are osteoclasts. Cancer. 1988; 62:1139-45.
31. Lucas RB. Pathology of tumors of oral tissues. Edinburg Scotland: Churchill Livingstone; 1984.
32. Regezi JA, Sciubba JJ, Jordan RCK. Oral Pathology Clinical Pathologic Correlations. 4 Ed. New Delhi: Elsevier; 2003.
33. Soskolne WA. Some Observations on the Pathogenesis and Morphology of Giant Cell Granulomas Proc. roy. Soc. Med. 1972; 65.
34. Anwar Ul Haque and Ambreen Moatasim . Giant Cell Tumor of Bone: A Neoplasm or a Reactive Condition?. Int J Clin Exp Pathol. 2008; 1:489-501.
35. Kumar V, Abbas, Fausto, Aster. Robbins and Cotran Pathologic Basis of Disease.8th ed. Philadelphia: Elsevier; 2010.
36. Rosai J, Ackermann LV. Surgical Pathology. 10th ed. St. Louis; CV Mosby (Elsevier); 2011.
37. Tronstad L. Root resorption- etiology, terminology and clinical manifestations. Endod Dent Traumatol. 1988; 4(6):241-52.
38. Neville BW, Damm DD, Allen CM, Bouquot JE. Oral and Maxillofacial Pathology. 3 Ed. New Delhi: Elsevier; 2010.
39. MacLauchlan S, Skokos EA, Meznarich N, Zhu DH, Raoof S, Shipley JM, et al. Macrophage fusion, giant cell formation, and the foreign body response require

matrix metalloproteinase 9. J Leukoc Biol.2009; 85:617–26.

40. Barnes L, Eveson JW, Reichart P, Sidransky D. World Health Organization classification of Tumours. Pathology and genetics of head and neck tumours. Lyon; IARC Press, 2005.

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