

# Classification of Giant Cell Lesions of the Oral Cavity: A Fresh Perspective

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## ABSTRACT

**Introduction:** Multinucleated giant cells are often encountered in oral lesions. An understanding of the histogenesis of these giant cells can give us an insight on the pathologic process in progress. Traditional classifications have placed little importance on the type or histogenesis of multinucleated giant cells in grouping these lesions.

**Objectives:** (a) To classify giant cell lesions based on the type and histogenesis of giant cells. (b) To establish the rationale for the proposed classification by reviewing recent research evidences with respect to histogenesis of multinucleated giant cells and related oral lesions.

**Materials and methods:** Scientific databases (PubMed and Google scholar) were searched for the literature using key words – giant cells, oral lesions, and histogenesis. Relevant articles were selected for review. A descriptive review was done.

**Results:** Giant cell lesions were classified based on the type of giant cells present. The rationale for this classification was based on the recent research findings regarding the histogenesis of giant cells.

Giant cells containing oral lesions were broadly identified as:

- Epithelial-derived viral-induced multinucleated giant cell containing lesions
- Monocyte/macrophage-derived giant cell containing lesions
- Tumors with giant cells.

**Conclusion:** The presence and the characteristic morphologic patterns of multinucleated giant cells are pathognomonic in the formation of giant cell lesions. An awareness regarding the biological mechanisms involved in the formation of these lesions is important for the prompt diagnosis and appropriate management of these lesions.

**Keywords:** Giant cells, Histogenesis, Multinucleated, Oral cavity.

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## INTRODUCTION

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.<sup>1,2</sup> An epidemiological study done by Mohajerani et al<sup>3</sup> has reported that 6.36% of the oral biopsies received in their lab were multinucleated giant cells containing lesions. Multinucleated giant cells are easily recognizable in histologic sections. Their presence is often pathognomonic and provides vital clues in the diagnosis of various oral lesions. The histogenesis of these multinucleated giant cells can provide us with an understanding on the pathologic process involved in the lesions.<sup>2</sup>

Classifying oral lesions with giant cells has always been problematic.<sup>1</sup> Traditionally, giant cell lesions of oral cavity have been classified with little importance based on the type or histogenesis of multinucleated giant cells present in the lesions.<sup>2,4</sup>

The aim of this study is to review the recent molecular evidences regarding the histogenesis of multinucleated giant cells and pathologic mechanisms of related oral lesions. We have also proposed a new classification for giant cell lesions of oral cavity based on the type and histogenesis of giant cells.

## BASED ON THE TYPE OF GIANT CELLS PRESENT, GIANT CELL LESIONS CAN BE CLASSIFIED AS FOLLOWS

- Epithelial-derived viral-induced multinucleated giant cell containing lesions
  - Tzank giant cells – herpes simplex
  - Tzank giant cells – herpes zoster
- Monocyte/macrophage-derived giant cell containing lesions
  - 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
  - Osteoclastic giant cell containing lesions
    - Lesions with osteoclastic giant cells being the primary pathologic cells
    - Paget's disease

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- Lesions with reactive osteoclastic giant cells formed secondarily by the activation of lesional stromal cells
  - Peripheral and central giant cell granulomas, cherubism, and aneurysmal bone cyst (ABC)
  - Fibrous dysplasia, brown tumor of hyperparathyroidism
- Touton giant cells
  - Xanthoma, Xanthogranuloma, fibrous histiocytoma
- Tumor giant cells
  - Tumors where giant cells are pathognomonic
    - Giant cell fibroma, Hodgkin's lymphoma
  - Other anaplastic malignancies.

**RATIONALE FOR THE PROPOSED CLASSIFICATION OF GIANT CELL LESIONS OF ORAL CAVITY**

**Epithelium-derived Viral-induced Multinucleated Giant Cells**

Human herpes virus and varicella zoster virus are all DNA viruses belonging to human herpes family.<sup>5</sup> Both viruses are transmitted through saliva and infect skin and mucosa. They produce painful vesicles in the affected areas. The infected cells exhibit acantholysis, nuclear clearing, and ballooning degeneration.<sup>6</sup> The infected cells express viral proteins on their cell membrane, which induce the cells to fuse with one another to form multinucleated giant cells.<sup>7,8</sup>

**Monocyte-derived Multinucleated Giant Cells**

Monocytes are incompletely differentiated bone marrow-derived cells seen in circulation. These cells are capable of settling in the tissues to undergo further differentiation and maturation.<sup>9</sup> They are found to be the precursors of macrophages and source of different types of giant cells.<sup>9,10</sup> Various monocyte-derived giant cells include osteoclasts, foreign body giant cells, Langhans giant cells, and Touton giant cells.<sup>10</sup>

**Inflammatory Granuloma-associated Giant Cells**

Granulomatous reaction is described as a distinct type of chronic inflammatory reaction associated with type IV hypersensitivity, which occurs against persistent or nondegradable antigens like microorganisms, foreign bodies, and unknown antigens.<sup>11</sup> Granuloma is a focus of microscopic aggregation of epithelioid macrophages and few giant cells surrounded by a collar of lymphocytes.<sup>12</sup>

The origin and mechanism of formation of these granuloma-associated giant cells were studied by Postlethwaite et al.<sup>13</sup> They recognized that heat labile

proteins released from stimulated T lymphocytes induced monocyte precursors to form multinucleated giant cells. These proteins were later recognized as T cell-derived cytokines.<sup>10</sup>

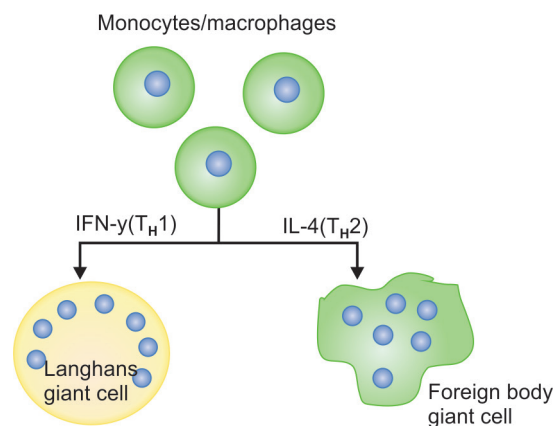
Helper T cells are differentiated into subsets of effector cells as Th1 and Th2. These subsets produce their own distinct sets of cytokines and therefore, can induce distinct effect or functions.<sup>9</sup> Th1 helper cells are associated with activation of macrophages in microbial infections, while Th2 helper lymphocytes are involved with suppression and resolution of chronic inflammation.<sup>14</sup> The signature cytokine of Th1 subtype is interferon (IFN)-gamma. The Th2 subsets of T lymphocytes produce cytokines like interleukin (IL)-4 that antagonize the actions of Th1-derived cytokine, IFN-gamma.<sup>9</sup> Various *in vitro* tissue culture experiments have found that the cytokine profiles present in chronic granulomas determine the morphology of giant cells formed in these lesions.<sup>11</sup> Hence, identifying the multinucleated giant cell types can provide us with a clue to the pathologic process under progression.

**Langhans Giant Cells**

The presence of poorly degradable or particulate antigens, especially microorganisms, initiates a hypersensitivity reaction and produces a type of granuloma called immune granuloma. These granulomas are histologically presented as solid collection of epithelioid macrophages with few Langhans giant cells bordered by a collar of lymphocytes. These granulomas are seen in response to the presence of microbial antigens as in tuberculosis, leprosy, late syphilis, deep fungal infections, or to unknown antigenic stimuli as in sarcoidosis and orofacial granulomatosis.<sup>12</sup> The Langhans giant cells associated with these granulomas have a characteristic horseshoe-shaped arrangement of the nuclei at one pole. They are traditionally considered to be a fusion product of epithelioid macrophages.<sup>7,15</sup>

Recent evidences have shown that Langhans giant cells are monocyte-derived and their formation is induced by the presence of cytokine IFN-gamma, the signature cytokine of Th1 subtype of helper T lymphocytes. Hence, it is obvious that granulomas with Th1 cytokine profile will have Langhans giant cell formation<sup>11</sup> (Fig. 1). Th1 differentiation pathway is known to be formed in response to the presence of microbes or other antigens in order to facilitate their destruction.<sup>9</sup>

New experimental studies have shown that when monocytes mature to macrophages they acquire phagocytic function but lose bactericidal activity.<sup>16</sup> They were also found to lose the ability to fuse together to form giant cells. When Most et al<sup>11</sup> co-cultured matured macrophages with monocytes, macrophages were



**Fig. 1:** Mechanism of multinucleated giant cell formation in inflammatory granulomas

found to fuse preferentially with monocytes rather than with other macrophages to form multinucleated giant cells. This giant cell formation provided macrophage with bactericidal enzymes via monocyte fusion in order to destroy the intracellular pathogens resistant to macrophage killing. These experimental findings challenge the traditional belief that Langhans giant cells are formed by the fusion between epithelioid macrophages. Langhans giant cells containing immune granulomas are characterized by a Th1 cytokine profile.<sup>7,15</sup>

### Foreign Body Giant Cells

Inert foreign bodies initiate a tissue response in the form of foreign body granuloma. This granuloma is characterized by the focal collection of epithelioid macrophages and giant cells are seen apposed or encompassing the foreign body.<sup>12</sup>

Foreign body giant cells are multinucleated giant cells associated with foreign body reaction. The nuclei are seen scattered throughout the cytoplasm. They are usually seen when foreign material is too large for phagocytic removal by the macrophage.<sup>7</sup> Experimental evidences have shown that cytokines produced by Th2 helper T lymphocytes, which are involved in the resolution of chronic inflammation are responsible for foreign body giant cell formation. *In vitro* tissue culture experiments done by McNally et al<sup>17</sup> showed that when monocyte cultures were provided with IL-4, foreign body giant cell formation was initiated and Langhans giant cell formation was inhibited (Fig. 1). Th2 helper cell-mediated immunity is known to be concerned with down regulation of inflammatory response in chronic granulomas. Hence, many researchers have hypothesized that foreign body giant cells are concerned with down regulation of local macrophage-derived inflammatory reaction by scavenging inflammatory products that would otherwise damage host tissue.<sup>9,14,17</sup>

### Osteoclastic Giant Cells

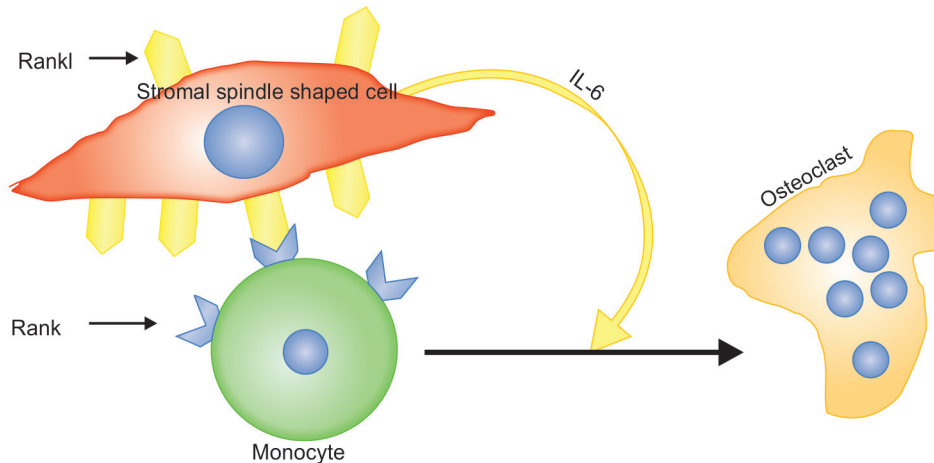
Osteoclasts are monocyte-derived multinucleated giant cells responsible for bone resorption.<sup>12</sup> The monocytic progenitor cells of osteoclasts have cell surface receptors called receptor activator of nuclear kappa-B (RANK). The proteins required to activate the monocyte receptor RANK are on the cell surfaces of osteoblasts and are called receptor activator of nuclear kappa-B ligand (RANKL). The RANKL present on osteoblasts activates the receptor RANK on monocyte progenitors, facilitating monocyte fusion to form multinucleated osteoclasts.<sup>18</sup> Giant cells associated with various giant cell lesions of head and neck area were found to be of osteoclastic lineage. The etiology and pathogenesis behind giant cell formation in these disorders are often varied.<sup>19</sup> Cytokines like IL-1, tumor necrosis factor (TNF $\alpha$ ), and IL-6 are found to promote osteoclastogenesis and osteoclast resorption.<sup>20</sup>

### Lesions with Osteoclastic Giant Cells being the Primary Pathologic Cells

*Osteoclastic giant cells associated with Paget's disease (Osteitis deformans):* Paget's disease is an osseous dysplasia characterized by rapid remodeling of bone throughout the skeleton resulting in distortion and weakening of the affected bone.<sup>6</sup> It is usually a disease of elderly. Recent investigations have shown that the primary cellular abnormality resides in the osteoclastic functioning.<sup>21,22</sup> Paget's disease is known to have a multifactorial etiology. Genetic mutations and environmental factors like viral infections were found to play a role in its development.<sup>23</sup>

Mutations in the gene coding for sequestrome 1 (also called p62) were found in many cases of Paget's disease. This gene in normal state was found to exert a regulatory control over osteoclastogenesis via RANKL signaling. A mutation to this gene leads to increased osteoclastogenesis and bone resorption as seen in Paget's disease.<sup>24</sup>

The osteoclasts, osteoblasts, and other marrow stromal cells of bone affected by Paget's disease showed an increased IL-6 production. Interleukin-6 is a known stimulant of osteoclastic differentiation.<sup>25,22</sup> The osteoclasts found in Paget's lesions are large, have increased number of nuclei, high resorbing capacity, secrete high levels of IL-6, and show increased response to 1, 25 dihydroxyvitamin D<sub>3</sub> and RANKL stimulation.<sup>21</sup> Osteoclasts in Paget's disease were also found to have nucleocapsid proteins of paramyxovirus. These virally infected osteoclasts were found to secrete high levels of IL-6.<sup>22</sup>



**Fig. 2:** Mechanism of osteoclast formation from monocytes by lesional spindle shaped cells

### *Lesions with Reactive Osteoclastic Giant Cells formed secondarily by the Activation of Lesional Stromal Cells (Fig. 2)*

*Peripheral and central giant cell granulomas, cherubism, and ABC:* Giant cell granulomas of the jaws are tumor-like reactive lesions occurring either peripherally on gingiva or as a central destructive lesion. They are considered to be formed from the periodontal ligament, periosteum, or from the central part of bone. Jaffe tried to distinguish between the less aggressive giant cell lesion of the jaw bones as giant cell granuloma and the more aggressive giant cell lesions of long bones as giant cell tumor or osteoclastoma.<sup>6,26</sup> Giant cell tumors are usually seen in femur and tibia.<sup>4</sup>

Cherubism is another giant cell containing centrally destructive pathology of jaw bones. It is a pediatric nonneoplastic hereditary bone lesion affecting the jaws bilaterally and symmetrically.<sup>6</sup>

All these jaw lesions have almost similar appearing histological picture. They are characterized by cellular collagenous stroma containing spindle-shaped cells and numerous multinucleated giant cells. Foci of hemorrhage and hemosiderin pigments are also seen.<sup>19,26</sup>

Another giant cell containing bone pathology with histological similarity is ABC. There are two types of ABCs: Aneurysmal bone cyst formed de novo are called primary and the ones found as areas within benign or malignant bone tumors are called secondary ABCs. Aneurysmal bone cyst was thought to be formed by local circulatory disturbances leading to increased venous pressure, dilatation of vascular network with resultant resorption of bone. But recent molecular evidences have shown that chromosomal aberrations are consistently present in primary ABCs.<sup>27</sup> Oliveria et al study of the genetic alterations in primary ABCs found that translocation of 17p13 was present in primary ABCs and it places USP6 oncogene under the regulatory influence of highly active CDH11 promoter gene. This

genetic aberration was absent in the so-called secondary ABCs. Fluorescent in situ hybridization (FISH) studies showed that these genetic alterations were seen within the spindle cell population of the lesional tissue and not on the multinucleated giant cells. Based on these current research findings, primary ABCs are now considered to be mesenchymal neoplastic disease characterized by spindle cell proliferation exhibiting USP6 or CDH11 genetic aberrations. The so-called secondary ABCs are considered to be just nonspecific morphologic patterns of various non-ABC tumors.<sup>28</sup>

Liu et al published the molecular characteristics of the cells involved in giant cell lesions of the jaws like peripheral and central cell giant granulomas, cherubism, and ABCs. They reported that giant cells in these pathologies were positive for H<sup>+</sup>ATPase, carbonic anhydrase II, cathepsin K, matrix metalloproteinases-9, tartrate-resistant acid phosphatase – all markers of osteoclastic lineage. The *in situ* hybridization studies revealed that multinucleated cells were positive for RANK confirming their osteoclastic lineage, but the spindle-shaped lesional stromal cells were positive for RANKL. This evidence shows that spindle-shaped stromal cells are of early osteoblastic differentiation and facilitate the formation of giant cells osteoclastic lineage via RANK–RANKL interaction.<sup>19,29</sup>

When the expression of a proliferative marker like PCNA was evaluated in these lesions, it was found that the giant cells were negative while spindle-shaped stromal cells were positive. This result shows that spindle-shaped stromal cells are the proliferating tumor cells responsible for the biological activity of these pathologies. The multinucleated giant cells are nonproliferative and are reactive in nature.<sup>19,29</sup> The precursor cells for osteoclast formation were found to be recruited from monocytes from the peripheral blood by the chemo-attractants released from the spindle-shaped stromal cells.<sup>30</sup>



**Osteoclastic giant cells of fibrous dysplasia:** Fibrous dysplasia is a benign fibro-osseous lesion characterized by focal bone lesions occurring in single or in multiple sites. In some cases the bone lesions are accompanied with endocrine and skin pigment disorders.<sup>6</sup> Mutations of GNAS1 gene that codes for alpha subunit of G protein were found to be responsible for fibrous dysplasia. Mutated alpha subunit of G protein keeps the downstream adenylyl cyclase in a constant stimulated state, leading to the overproduction of cyclic adenosine monophosphate (cAMP). The mutation containing dysplastic cells was found to be spindle-shaped alkaline phosphatase positive and preosteoblastic in nature. These dysplastic cells were highly proliferative and poorly differentiated. A mixed population of these defective preosteoblastic cells and nonmutated cells leads to the rapid deposition of immature poorly organized bone of fibrous dysplasia.<sup>31</sup>

Sometimes unusually large number of osteoclasts and evidence of resorption can be seen in fibrous dysplasias.<sup>31</sup> Studies done by Riminucci et al have shown that GNAS1 mutation containing preosteoblastic cells secrete cytokine, IL-6 three times more than normal stromal cells. Hypersecretion of IL-6 is attributed to the increased levels of cAMP in dysplastic cells.<sup>32</sup> Interleukin-6 is a factor known to stimulate osteoclast differentiation and induce bone resorption.<sup>20</sup>

**Osteoclastic giant cells of hyperparathyroidism-induced brown tumor:** Craniofacial bone lesions seen in both primary and secondary hyperparathyroidism are currently classified as fibro-osseous lesions under the heading of metabolic disorders.<sup>33</sup> Various osseous lesions develop in this metabolic disorder due to the excess secretion of parathyroid hormone (PTH). The characteristic osseous lesion developed due to removal of calcium salts in persistent hyperparathyroidism is "brown tumor." The histopathology of this lesion resembles a central giant cell granuloma. It is characterized by proliferation of a vascular granulation tissue with numerous osteoclastic giant cells, abundant hemorrhage, and hemosiderin deposits.<sup>6</sup>

Parathyroid hormone is associated with the maintenance of calcium levels in the body. It is a known activator of osteoclasts. The osteoclastic activation of PTH is mediated via osteoblasts since osteoclasts do not have any receptors for PTH.<sup>34</sup> Tissue culture studies have shown that PTH can stimulate osteoclasts only in the presence of osteoblasts. Parathyroid hormone was found to activate the osteoblasts via adenylyl cyclase. The activated osteoblasts were found to secrete cytokines that activate and recruit osteoclasts for bone resorption.<sup>35</sup> Initial response to PTH stimuli is functional activation of existing osteoclasts mediated through IL-6 secretion. Macrophage colony stimulating factor is needed for the further osteoclastic recruitment and differentiation. Other cytokines like

leukemia inhibitory factor and IL-11 can also mediate bone resorption in response to PTH stimuli.<sup>36,37</sup>

### Touton Giant Cells

These giant cells are described as multinucleated lipid laden cells. The nuclei are arranged in a circular pattern around a central eosinophilic area. Vacuolated cytoplasm is seen between the nuclei and cell membrane.<sup>38</sup> These giant cells are usually found in lesions containing lipid deposits like xanthoma and xanthogranuloma. They are also seen in fibrous histiocytomas. These giant cells are formed by the fusion of macrophages and are positive for histiocytic markers like CD68, lysozyme, alpha-1 antitrypsin, and factor XIIIa.<sup>2</sup>

### Tumor Giant Cells

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.<sup>2</sup>

#### *Tumors where Giant Cells are Pathognomonic*

**Giant cell fibroma:** They are considered as a distinct type of fibroma and are often described as a benign fibroblastic tumor.<sup>6</sup> On the contrary, numerous recent reports consider them as a reactive fibrous hyperplasia of oral cavity.<sup>39,40</sup> These fibromas are characterized by stellate-shaped fibroblasts and multinucleated giant cells.<sup>40</sup> These giant cells were found to be negative for cytokeratin, S100, leukocyte common antigen, CD68, desmin. They were positive only for vimentin confirming that they are fibroblastic in origin. These giant cells were negative for proliferative markers like Ki67.<sup>39</sup>

**Hodgkin's lymphoma:** It is a group of lymphoid neoplasms occurring at a single node or group of nodes and spreading to anatomically contiguous nodes. These tumors are characterized by pathognomonic tumor giant cells called Reed–Sternberg cells. They are large cells with multiple nuclei or single nucleus with multiple lobes resembling the "owl's eye." They are derived from germinal center B cells. These giant cells induce the accumulation of reactive lymphocytes, histocytes, and granulocytes by secreting appropriate cytokines.<sup>12</sup> Identifying Reed–Sternberg cells is a requisite for diagnosing these lesions. They are reported to be present in oral sites also.<sup>6</sup>

#### *Other Anaplastic Malignancies*

Tumor giant cells can be encountered in malignancies in oral cavity as a consequence of anaplasia.<sup>12</sup> Formation of

multinucleated giant cells in malignancies can be attributed to the newly discovered cellular events in tumor cells like mitotic catastrophe.<sup>41</sup> The growth of malignant tumor cells that have accumulated mutations and genomic material (aneuploid) often evokes an oncosuppressive cellular mechanism called mitotic catastrophe. This event is characterized by unique nuclear alterations, resulting in the formation of multinucleated giant cells.<sup>42</sup>

**CONCLUSION**

Presence of multinucleated giant cells in oral lesions is an easily identifiable feature in histological sections. Knowledge on the histogenesis of these giant cells will help us to understand the pathologic process involved in the associated oral lesions. Prompt and accurate diagnosis of these lesions is important for its appropriate management. Hence, pathologists should be aware of the biological mechanisms involved in the formation of these lesions.

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