ABSTRACT
The usual histological picture composed of the cell with presence of single nucleus. Rarely, Multinucleated Giant Cell are encountered. There are various physiological and pathological events in which multinucleated giant cells are evident. It is important to understand mechanism of formation and role of giant cells in such physiological and pathological events. In present review focus on the nature of various types of giant cells and various pathological lesions in which the giant cell are encountered with its histogenesis.

KEYWORDS: Various types of giant cells and various pathological lesions.

INTRODUCTION
In histology and histopathology, it is general that cells normally contain a single nucleus. This broad generalization is broken in a relatively small number of specific circumstances. These are the circumstances in which giant cell are encountered. A giant cell can be described as an unusually large, huge or gigantic cell; as a large multinucleated often phagocytic cell, cell with more than one nucleus, a multinucleated mass of cytoplasm that is not separated into cells.[1]

Some tissues regularly contain cells in which several nuclei share the same cytoplasm like skeletal muscle, placenta and bone. The occurrence of multinucleated giant cells elsewhere is always abnormal.[2]

Muller J (1838) discovered the giant cell,[2] some years later, Virchow and Langhans discussed their nature. Lambert A (1912) observed the formation of multinucleate giant cells from wandering mononuclear cells, while the Lewises reported the transformation of the mononuclear blood cells of lower vertebrates into giant cells in hanging drop cultures. Since then, several other investigations have provided further evidence for the derivation of giant cells from mononuclear phagocytes.[3]

Giant cells can be classified into several morphological variants depending upon the Arrangement and composition of organelles, functional characteristics and pathology involved.

I. Classification based on arrangement, composition of organelles and function.

A. Haythorn (1929)[4]
(1) Langhans giant cells
(2) Foreign body giant cells
(3) Osteoclasts
(4) Megakaryocytes
(5) Muscle giant cells
(6) Giant cells of nervous tissue
(7) True tumor giant cells.

B. Quinn MT and Schepetkin IA (2009)[5]
1. Foreign body giant cells
2. Langhans giant cells
3. Touton giant cells
4. Osteoclast like cells
5. Osteoclasts.

II. Classification based on functional characteristics
Chattopadhyay (1995)[6]
1. Damaged striated muscle fibres
   a. Regenerating sacrolemma cells in damaged voluntary muscle.
   b. Aschoff giant cells in heart muscle (fused myocardial macrophages).
2. Fused fibroblasts (as in giant cell fibroma)
3. The osteoclast
4. Tumor giant cells
   a. Reed-stern berg cells in Hodgkin’s lymphomas.
   b. Giant cells in central giant cell granuloma
   c. Giant cells in other tumors eg. Carcinoma
5. Fused cells due to viral infections.
   a. Epithelial giant cells as in HSV infection.
   b. Connective tissue cells as in Measles (Warthin Finkeldey cells).

6. Fused macrophages
   a. Due to reaction to foreign bodies (exogenous or endogenous materials) e.g. foreign body giant cell with scattered nuclei.
   b. Due to reaction to organism as in tuberculosis (Langhans’ giant cell) and fungal infections
   c. Touton giant cells of xanthoma.

III. Classification based on pathology involved
A. Cotran, Kumar and Robbins (1994)[7]

   1. Giant Cells In Inflammation
      a) Foreign Body giant cells
      b) Langhan’s giant cells
      c) Touton giant cells
      d) Aschoff giant cells

   2. Giant Cells In Tumor
      a) Tumor giant cells
      b) Reed-Sternberg cells
      c) Giant cell tumor of bone.

B. Varghese I and Prakash A (2011)[1]

   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.
   5. Osteodystrophic lesions: Noonan-like multiple giant cell lesion syndrome.

IV. Deepu G Mathew et al.[8] also put forth the new prespective of classification 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
     — Tzanck giant cells – herpes simplex,
     — Tzanck giant cells – herpes zoster

   • Monocyte/macrophage-derived giant cell containing lesions
     1. 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

2. Osteoclastic giant cell containing lesions
Lesions with osteoclastic giant cells being the primary pathologic cells - Paget’s disease
- 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
- 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.

Such classification helps to understand correlation between the pathogenesis of the lesion and role of multinucleated giant cells in the pathogenesis.

ORAL LEPROSY
Leprosy oral lesions are common in the lepromatous form. Oral lesions are the late manifestation. The oral lesions in leprosy are generally asymptomatic. Many times occurrence is secondary to nasal changes. The most frequently affected site is the hard palate.[9]

ORAL ACTINOMYCOSIS
Cervicofacial Actinomycosis is the most common form of actinomycosis. The sites most commonly involved include the submandibular space, cheek, parotid gland, teeth, tongue, nasal cavity, gingival and oral space.[10]

ORAL SARCOIDOSIS
Oral involvement generally appears in patients with chronic multisystem sarcoidosis and occurs in the acute stage. The oral lesions may be solitary, multiple or part of a generalized disease. In some cases, oral involvement is the first or only, manifestation of the diseases and appears as a non tender well-circumscribed brownish red swelling.[11]

The presence of poorly degradable, particulate antigens, especially microorganisms initiates a hypersensitivity reaction. Such reaction produces 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.[12]

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.[13]
CENTRAL GIANT CELL GRANULOMA
It as an intraosseous lesion consisting of predominantly cellular fibrous tissue. Cellular fibrous tissue composed of multiple foci of hemorrhage, aggregations of multinucleated giant cells and occasionally trabeculae of woven bone.\[^{15}\]

PERIPHERAL GIANT CELL GRANULOMA
The PGCG also known as giant cell reparative granuloma, or giant cell hyperplasia, are reactive exophytic lesions found in the oral cavity. PGCG’s may present itself as polypoid or nodular lesions, predominantly bluish red with a smooth shiny or manillated surface. They are variable in size, though reportedly rarely exceed 2 cm in diameter, and are generally soft or rubbery to touch. They are basically asymptomatic, unless they interfere with occlusion and affect largely the lower jaw in the premolar and molar regions.\[^{16}\]

Giant cell granulomas of the jaws are tumor-like reactive lesions occurring either peripherally on gingival or as a central destructive lesion. They are considered to be formed from the periodontal ligament, periosteum, or from the central part of bone. Cytokines like IL1, tumor necrosis factor (TNFα), and IL-6 are found to promote osteoclastogenesis and osteoclast resorption.\[^{17}\]

GIANT CELL FIBROMA
Giant cell fibroma was named for its characteristically large, stellateshaped, mononuclear and multinucleated giant cells. It presents clinically as an asymptomatic raised lesion, 1 cm or smaller in diameter. It may be pedunculated or sessile and is found most commonly on the gingiva.\[^{18}\]

The giant cells in giant cell fibroma shows fibroblast phenotype and are large atypical fibroblasts.\[^{19}\]

OSTEOSARCOMA
Approximately 7% of all primary OS arise in the jaw bones.\[^{17}\] The mandible is more commonly involved than the maxilla (1.5:1) Consideration should be given to the possibility of oral metastases in patients with known primary malignant disease and biopsy is essential for establishing the diagnosis.\[^{20}\]

RHABDOMYSARCOMA
Rhabdomyosarcoma (RMS) is a mesenchymal malignant neoplasm that exhibits skeletal muscle cells with varying differentiation degrees. It occurs most often in the head and neck region, genitourinary tract, retroperitoneum and to a lesser extent the extremities. In the head and neck, the most frequently affected sites are orbit, paranasal sinuses, soft tissues of the cheek and the neck. In the oral cavity the most common sites are tongue, palate and buccal mucosa.\[^{19}\] The diagnosis of RMS is confirmed through biopsy of the primary tumor.\[^{21}\]

HODGKIN'S LYMPHOMA
Lymphomas are the second most frequent malignancies affecting the head and neck region after carcinomas. Hodgkin's lymphoma is a disease affecting primarily lymph nodes with secondary extranodal spread. It accounts for 1 - 5% of head and neck tumors.\[^{20}\] Immunophenotypically, Reed - Sternberg cells are positive for CD15/CD30 and negative for CD45/CD20 both in nodal and extra nodal disease.\[^{22}\]

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.\[^{13}\]

ANEURYSMAL BONE CYST
ABC is characterized by the replacement of the bone by spongy fibro-osseous tissue, and is a locally destructive and multicystic lesion filled with blood.\[^{22}\] Only 2% of ABCs are found in the head and neck, with 66% of these being located in the mandible.\[^{23}\] Histologically, the ABC is characterised by large blood-filled spaces which do not have an endothelial lining. Instead, the cyst wall and septa are made up of fibroblasts, myofibroblasts, histiocytes, congested vessels, osteoblasts, osteoid, bone and degenerated calcifying fibromyxoid tissue. Surgery and curettage of the cavity is the main treatment of ABC.\[^{23}\]

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, primary ABCs are now considered to be mesenchymal neoplastic disease characterized by spindle cell proliferation exhibiting USP6 or CDH11 genetic aberrations.\[^{24}\]

HYPERPARATHYROIDISM
HPT is divided into primary, secondary and tertiary categories. Classic skeletal lesions, which are bone resorption, bone cysts, brown tumours and generalized osteopenia, occur in less than 5% of cases. The ribs, clavicles, pelvic girdle, and the mandible are the most often involved bones.\[^{25}\]

Parathyroid hormone is associated with the maintenance of calcium levels in the body. It is a known activator of osteoclasts. As the increased level of parathyroid hormone leads to formation of the number osteoclasts resulting in multinucleated giant cell.\[^{26}\]

CHERUBISM
Cherubism, or familial intraosseous fibrous expansion of the mandible, is a disease characterised by the presence of giant cells and fibrous tissue proliferation.
Histopathology reveals numerous multinucleate giant cells which are tartrate resistant acid phosphatase positive (characteristic of osteoclast). These cells are scattered in between mononuclear spindle cells. Eosinophilic capping of vessels is specific for cherubism.\textsuperscript{27}

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+ATPase, carbonic anhydrase II, cathepsin K, matrix metalloproteinases-9, tartrate-resistant acid phosphatase – all markers of osteoclastic lineage.\textsuperscript{28}

PAGET’S DISEASE

It is a localized disorder of bone remodelling characterized by an increase in osteoclast-mediated bone resorption and a compensatory increase in new bone formation. PDB is characterized by increased bone turnover.\textsuperscript{29} Recent investigations have shown that the primary cellular abnormality resides in the osteoclastic functioning, thus increased atypical osteoclast number results in presence of giant cells.\textsuperscript{30}

FIBROUS DYSPLASIA

It is the replacement of normal bone with fibrous tissue causing painless expansile lesions that impair cosmetic and structural function of bone. They constitute 7% of all nonmalignant bone tumors and may be either monostotic or polyostotic. The monostotic form is more commonly found in the facial skeletal region. The normal bone is replaced by tissue that is more radiolucent, with a grayish “ground-glass” pattern that is similar to the density of cancellous bone but is homogeneous, with no visible trabecular pattern.\textsuperscript{31}

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.\textsuperscript{32}

REFERENCES

22. Malis DD, Mo.at D, McGarry GW. Isolated nasopharyngeal Hodgkin’s disease presenting as


