Involvement of Giant Cells in the Development of Bone Tumor

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Abstract

Osteosarcoma (OS) or Osteogenic sarcoma is a commonly occurring primary bone tumor that occurs in young age including adolescence age group and contributes approximately about 20% of all the other sarcomas. Giant cell rich osteosarcoma (GCRO) is considered as a rare sub-type in the category of primary osteogenic sarcoma. GCRO sarcoma possesses giant cells that look like osteoclasts in abundance and insufficient amount of osteoids are also present. GCRO excludes several features related to classical radiographic aspects in conventional osteosarcomas. This results in its pivotal importance in recognition as a subspace of osteosarcoma and its distinction from other meticulously related tumor in bone. GCRO can be either benign or malignant osteolytic tumor that can be observed on the plain radiographs. Furthermore, giant cell tumor (GCT) whether benign or malignant, in case of histological differentiation is challenging and is highly important because of its aggressively fatal consequences. The GCT contributes nearly 5% of primary bone and the tumor bone is commonly found in the end points of the long bone. In this review, we attempted to recognize and summarize the involvement of giant cells in the development of bone tumor and describe some important gene expressions to get an insight about the strategies to control this type of bone tumor.

Keywords: Osteosarcoma; Giant cell tumor; Giant cell tumor of bone; Giant cell tumor stromal cells; p63; Histone H3.3; RANK ligand

Abbreviations: OS: Osteosarcoma; GCRO: Giant Cell Rich Osteosarcoma; GCT: Giant Cell Tumor; GCTSC: Giant Cell Tumor Stromal Cells; RANK: Receptor Activator of Nuclear Factor Kappa B; RANKL: RANK Ligand; MFR: Macrophage Fusion Receptor; IHC: Immunohistochemistry; DC-STAMP: Dendritic Cell Specific Trans-Membrane Protein; GCTB: Giant Cell Tumor of Bone; M-CSF: Macrophage-Colony Stimulation Factor; PMMA: Polymethylmethacrylate; OPG: Osteoprotegerin

Introduction

Osteosarcoma (OS)

Osteosarcoma is enlisted among the most familiar types of malignant tumor of bone in adolescents and young adults. U.S. has the highest number of cases approximately four per million per year [1]. A recent report highlights a case of dominant type of sarcoma that gets unfolded osteosarcoma due to insufficient proof in data as per the reports [6]. The initial research studies consider the tumor to be much more cellular and reasonably vascularized and consisted of circular oval or somewhat spindle mono-nucleated cells containing huge conglomeration of giant cells with multiplex nuclei [7]. The stromal cells include faint cytoplasm possessing an indefinite extremity, a nucleus having an explicit nuclear membrane and a routinely protruding nucleolus. The multi-nucleated giant cells possess certain nuclei that are collateral to the nuclei in stromal cells, physically/biochemically and practicably resemble to osteoclasts. The giant cells of this type are usually observed in other several primary sarcomas related to bone, in conjunction with osteosarcoma, differentiated chondrosarcoma, uniform pleomorphic sarcoma, fibrosarcoma and leiomyosarcoma [8].

On the basis of demographics, osteosarcomas can be classified into two categories, primary and secondary. These are intramedullary or centrally positioned in long tubular bones and are of high grade mostly. Primary osteosarcoma is observed in highly young patients (10-20 years) and 75% cases occur before the age of 20 years due to some important locations called as the growth centers of the bone that are much more active during puberty/adolescence. These type of tumors are typically observed in the vital metaphyseal regions of long bones, showing an astonishing propensity for the knee involving around 60% of presence. Secondary osteosarcoma usually occurs in the old age and is commonly secondary to malignant decension in case of Paget disease, pervasive bone infarcts post-radiotherapy for other conditions, osteochondroma and osteoblastoma [4]. These tumors undergo a much wider dissemination including the combined scope of their underlying condition, and thus have a greater occurrence rate in flat bones, especially the pelvis that is the most suitable site for Paget disease. In case of clinical presentation, patients usually come up with bone pain and soft-tissue mass or swelling sometimes [5]. Osteosarcoma is diagnosed prominently once it shows up in its classic or conventional form. The emergence of osteoid directly by the tumor cells, called as tumor osteoid or malignant osteoid, is actually required for the high level diagnosis of osteosarcoma. The genetic contradictions are highly complex and variability is shown at a very high rate. The p53 analysis can be implemented to prognosticate the individual cases with the help of tumor tissue. Immunohistochemistry (IHC) cannot be applied in osteosarcoma due to insufficient proof in data as per the reports [6].

Giant cells (GCs)

The initial research studies consider the tumor to be much more cellular and reasonably vascularized and consisted of circular oval or somewhat spindle mono-nucleated cells containing huge conglomeration of giant cells with multiplex nuclei [7]. The stromal cells include faint cytoplasm possessing an indefinite extremity, a nucleus having an explicit nuclear membrane and a routinely protruding nucleolus. The multi-nucleated giant cells possess certain nuclei that are collateral to the nuclei in stromal cells, physically/biochemically and practicably resemble to osteoclasts. The giant cells of this type are usually observed in other several primary sarcomas related to bone, in conjunction with osteosarcoma, differentiated chondrosarcoma, uniform pleomorphic sarcoma, fibrosarcoma and leiomyosarcoma [8]. Giant cells are mostly composed of polyploid complements of
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fusion factor play an effective role in the formation and function of
dendritic cell specific trans-membrane protein (DC-STAMP) and a
phenotypic variation in multinucleated giant cell types is based on the
confined ambiance and the physicochemical nature of the source, to
which, the giant cell types and their monocyte/macrophage precursors
signal back [12]. According to recent reports on foreign body giant
cells and osteoclasts specifically, a number of common factors such as;
macrophage fusion receptor (MFR), an adhesion protein, vitronectin,
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mononuclear giant cell formation and function of foreign body. These giant cells can
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Giant cell tumor of bone (GCTB)

Giant cell tumor of bone (GCTB) being sectionally rapacious
neoplasm contributes to about 5% of the overall primary bone tumors.
This type of tumor plays a vital role in making an effective impact on
radiographic and histopathologic demonstrations involving distinctive
benign, malignant and metabolic abrasions rich in giant cells [15].
Giant cell rich osteosarcoma term was initially explained by Bathurst
and Sanekin in 1986 [16]. An unusual case of osteosarcoma occurs that
accounts for nearly 1-3% of overall cases in conventional osteosarcomas.
Conventional osteosarcoma is largely found in young adults. It mostly
shows up at the beginning of 20th year of life and almost about 60%
of the patients are of 25 years of age. Conventional osteosarcoma
shows a fervent tendency in the participation of elongated bones of
the appendicular skeleton; especially, distal femur, proximal tibia, and
proximal humerus [17]. Few reports elucidate malignancy in giant cell
tumor as a sarcoma that emerges in tumor of giant cells. A sarcoma
that emerges in a tumor linked to giant cells is considered as primary
malignant giant cell tumor and the one that emerges at the site of the
antecedently diagnosed tumor in giant cells is labeled as secondary
malignant giant cell tumor. Sarcomas that emerge in primary giant
cell tumor can be malignant fibrous histiocytoma or fibrosarcoma.
These can be secondary malignant giant cell tumor as well [18]. A new
category of secondary malignant giant cell tumor was reported which
described carcinosarcoma to be a malignant abrasion in case of giant
cell tumor. The tumor of giant cells of bone is usually seen in meta
epiphyseal area that gets developed post skeletal maturation [19].
In case of tumor formation at the starting point, mono-nuclear histiocytic
cells effectively play an important role at the encampment of the tumor
and fusion occurs to process multi-nucleated giant cells (MGCs) tumor.
The stromal cells of neoplastic tumor of giant cells express the activator
of receptor in nuclear factor κB ligand (RANKL) thus supporting the
unification with macrophage colony stimulating factor (M-CSF) that
acts as a cofactor [20].

Giant cell tumor in general consists of mononuclear histiocytic
cells, giant cells with multiple nuclei enclosed in mononcystic-histocytic
system and cells of neoplastic tumor that have high proliferation rate, also
known as giant cell tumor stromal cells (GCTSC) with no involvement in
the mononuclear-histiocytic system. A case in which solvable factors
from the GCTSCs help in the induction of multinucleated giant cell
formation from monocytes was demonstrated by Nishimura et al.
in 2005 [21]. These multinucleated giant cells possess characteristic
biomarkers evocative of osteoclasts [22]. The chemo-attraction of
mononuclear histiocytes as well as the development of multinuclear
giant cells is signaled by giant cell tumor stromal cells. GCTSC gene
expression indicates the early osteoblastic differentiation of stromal
cells and discrimination features of mesenchymal stem cells are also
shown in this case. GCT involves a lytic abrasion centralized in the
pinéal region but exclusively includes the metaphysical point and extends
to the adjoining articular cortex. Less than 2% of this region
can be seen in the metaphysis or diaphysis and all the lesions initiate in
the intramedullary region in the major long bones such as the femur
and tibia. These lesions become symmetric and centrally located with
the growth and are mostly eccentric [23,24].

Giant cell tumor of bone (GCTB) is known for being a primary
tumor of a bone as a special case possessing significant biological
characteristics in the form of three histological different types of cells
such as: Osteoclast like multi-nucleated giant cells, the spindle shaped,
fibroblast-like mesenchymal stromal cell, and a discoid morphology
called macrophage-like cells [25]. World Health Organization
categorizes this type of tumor as a benign one but this tumor shows
highly acute local aggressiveness, predisposition for local relapse
especially in spine, and uncommon metastasis [26]. GCTB is also
shown to exhibit malignant transformation like sarcomatous changes
due to the process of irradiation in case of primary treatment or
spontaneous malignant transformation irrespective of radiation
therapy. This tumor was described by Cooper in 1818, since then, the
understanding of GCTB has reached to suitable level, and till date,
a number of attempts have been exercised in order to describe the
prognostic parameters for GCTB [27]. A distinguished parallelism
has been observed between generalized cell types in bone tumor and
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clear strategy in bone tumor based on different factors such as tumor
loci, primary or secondary observation, based on the gender involved,
whether benign or malignant etc. The table cited below (Table 1) gives
a brief outlook about the normal cells as well as giant cells involved in
the tumor of bone based on certain factors.

Development of Giant Cell Tumor of Bone (GCTB)

p63 gene expression in GCTB

p63 gene is considered as one of the potential members of the
family of p53 tumor suppressor genes that is involved in the nuclear
expression in several different cell types like myoepithelial cells,
urothelium, squamous epithelium of mammary and salivary glands
and basal cells in prostate. The alteration observed in the expression
of a number of p63 target genes due to mutant-p53 protein shows high
level of intrusive conduct (Figure 1). The complex which consists of
p63, mutant p53 along with phosphor- SMAD2 alters the Cyclin G2 as
well as SHARP1 expression. Dicer expression arbitrated by p63 could get hampered if mutant p53 binds to Pin1, this leads to the enhanced metastases process in an in vivo model for tumor. The intervention shown by p63 in the repression of several genes including DEPDC1 (DEP domain containing 1) could be resisted by Mutant p53. The actual mechanism by which the proteins such as; Cyclin G2, DEPDC1, SHARP1, Dicer are inculpated in the process of invasion and metastasis are still under study [28].

The expression of p63 immuno-staining in the mononuclear cells of giant cell tumor was reported by Dickson et al. in 2008. This technique is highly useful to differentiate between giant cell tumor and other giant cell rich tumors, such as aneurysmal bone cysts, chondroblastoma and reparative giant cell granuloma [29]. Furthermore, no significance shown in case of gender, age and dominance or radiologic findings was reported earlier [30-34]. Meanwhile, eloquent distinctions between specific tissue or elapse and recurrence were observed with the help of statistical analysis. In this case, positive correlation was performed to check the involvement of extensor tendon, flexor tendon and joint capsule. In the method of identification of 20q11 amplifications in 55% of GCTB, genomic hybridization provides the data for various molecular models to help in the monoclonal neoplastic processes [35]. Other related data are helpful in suggesting the important role of p53 expression in case of 25% of GCTB. The osteoclastic giant cells possess the ability to enhance the bone resorption through cathepsin K and matrix metalloproteinase, thus, showing a potential evidence for the role of RANKL signaling in the pathogenesis of GCTB [36]. The p63 expression prominence determined in giant cell tumor present in a bone in contrast with other lesions rich in giant cells supports the role of giant cells. In a cross-sectional view, p63 immune-histochemical expression was checked in approximately about 100 giant cell rich lesions in a sequential manner that involved 31 giant cell related tumors present in bone, 14 cases of osteosarcomas consisted of 3 variants rich in giant cells, 18 aneurysmal cysts present in bone (consisting of one solid variant), 17 chondroblastomas, 8 fibromas

Table 1: Normal bone cells and giant cell bone tumor separated on the basis of factors such as; p63 gene expression, H3.3 mutation, RANKL and soft tissue recurrence.
is quite different from various types of bone lesions with osteoclastic giant cells that include chondroblasto, non-ossifying fibroma, brown tumor (hyperparathyroidism), giant cell reparative granuloma, primary ABC and osteosarcoma as well, and particularly the giant cell-rich type. The treatment result evaluation was mixed up with the fact that although most of the relapse occurs within 3 years of treatment, late recurrence of giant cell tumors, even after 15 years, has been shown to take place in the location where identified lesion had been surgically removed; others were shown to relapse as late as 42 years later [30].

**Histone H3.3 mutations in GCTB**

Histone H3.3 is encoded by two genes that are stationed in distinct loci. H3F3A is located on chromosome 1 and H3F3B is positioned on chromosome 17. The confinement of macroH2A to the managerial sites related to pluripotency genes has been reported recently, its diminution leads to the elevation of 25-fold related to the competence of reprogramming as well as escalation in the instigation regarding the genes that show pluripotency characteristics, which in-turn hints

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**Figure 1:** Interaction of different factors concomitantly and specifically highlighting the inhibition of the function of p63 by Mutant p53 that results in the alteration of gene expressions of several proteins including SHARP1, Cyclin G2, DEPDC1, Dicer and thus invasion and metastasis occur by the reprocessing of integrins and growth factor receptors.

**Figure 2:** Opposing roles of histone H3.3 in reprogramming. (A) The genes exhibiting pluripotency are present in a repressive chromatin environment in somatic cells. With the help of transient binding that occurs by a reprogramming factor to its binding site gives rise to histone H3.3 incorporation, which in turn helps to develop a highly compact chromatin structure and improved access of the binding site. The possibility of co-binding of Oct4, Sox2 and Klf4 and activation of the target pluripotency gene are increased by these chromatin modifications. (B) Increased levels of histone H3.3 mark the active genes. H3.3 is wiped off by the replication-dependent intervention of histone H3.1 at the time of DNA replication. The gene re-activation or silencing process is dependent on the suitable signals being created. The gradual silencing of the tissue-specific genes occurs along-with reprogramming process. However, increase the probability of H3.3 incorporation is shown with the help of high levels of expression in H3.3 and thus the memory enrichment of the somatic cell gene expression pattern takes place.
The establishment of mutations in H3F3A is one of the potential examples of operating diversifications, encoding histone variant H3.3, in pediatric tumors, exhibiting tremendously intermittent mutations that impinge the N-terminal tail of H3.3 and kicks off the amino acid substitution of lysine 27 to methionine (p.Lys27Met) and of glycine 34 to arginine or valine (p.Gly34Arg or p.Gly34Val). Adrienne Flanagan [52] studied giant cell tumor of bone exhibiting periodical mutations in H3.3 gene, which in turn results in the augmentation of MyoD expression, thus showing the persistence for almost up to 12 embryonic demarcations, irrespective of paucity in transcription process during the prescribed time span [46-50].

According to the recent studies, a distinguishing genetic modulation of GCT was observed, which acts as a leading mutation in the H3F3A gene of the family of histone 3.3A, 3A that is stationed on chromosome 1q21. This family is very important in the regulation of transcription, DNA replication and chromosomal cohesion. The DNA of 6 patients was analyzed in chondroblastoma and was observed that most of the cases witnessed point mutations in the H3F3B gene and also at the later stage, out of 53 cases of patients stimulated with GCT, s that 49 (92%) possessed missense mutations in the H3F3A gene. In 48 cases, the substitution was caused by GCT mutation in a glycine (Gly at codon 35 with tryptophan (trp), thus the p.Gly35Trp modulation was discovered. However, the substitution was noticed to take place with leucine (Leu), p.Gly35Leu. In one case. Point mutations delineated in GCT so far came up with the H3F3A modifications such as: p.Gly35Trp, p.Gly35Leu, p.Gly35Val, p.Gly35Met, p.Gly35GlU, while no mutation established in the H3F3B gene. This study is of diagnostic importance as GCT mainly consists of a huge group of multinucleated giant cells coordinated together in a fashionable manner according to the historical perspective and it can also be available at high level.
in other bone-related cancers. In case of highly accurate differential diagnosis, particularly in giant cell rich sarcomas, these alterations in the H3F3A gene, with a time-saving and highly cognizant nature play an important role to extricate GCT from tumors with resemblance in their histology [39].

Receptor activator of Nuclear factor Kappa-B Ligand (RANKL) in GCTB

RANKL/RANK signaling is considered as the backbone in the regulation of osteoclast formation, activation, and survival in the modeling and remodeling of bone as well as in the divergency of catabolic circumstances described by elevated bone turnover. Tumor necrosis factor-α (TNFα) superfamily comprises of around 40 members, the number of membrane or soluble receptors is found to be the same. RANKL has been found to be one of the potential members in the TNF-α superfamily (TNFSF11), binding to the membrane receptor called as, receptor activator of nuclear factor-kB (RANK). The clearly defined intracellular signal transduction occurs due to the effective activity in between RANK and RANK. This entire signaling process is managed with the help of an imitated receptor known as osteoprotegerin (OPG) [40] (Figure 3). OPG helps in the safeguarding of bone in case of exaggerated resorption by binding to RANKL and in turn intercepting the binding to RANK. In this way, the leading definitive of mass and strength in bone is credited to the contingent consolidation of RANKL and OPG [33]. Giant cell tumor mainly consists of neoplastic mononuclear stromal cells and reactive neoplastic multinucleated giant cells actively responsible for bone resorption. This process is mediated by interaction between receptor activator of nuclear factor-kB (RANK) expressed by giant cells and RANK ligand (RANKL) on stromal cells. The receptor activator of nuclear factor kappaB ligand (RANKL) discovery plays a marvelous role in the pathogenesis of GCTB [54].

It has been shown that the receptor activator of nuclear factor kappa-B ligand (RANKL) and its receptor RANK axis play a pivotal role in the development of GCTB. Mononuclear stromal cells express RANKL, which then binds to RANK on the surface of osteoclast-type multinucleated giant cells that results in the process of activation and proliferation of these giant cells. The exact role of RANKL is the result of the critical action of denosumab. Denosumab is a monoclonal antibody inhibitor of RANKL and is highly effective in limited clinical trials for blocking tumor progression in the patients which possess recurrent or unresectable giant cell tumors. It can be a potential anti-tumor agent for GCTB. The previous reports reveal that the post-denosumab GCTBs histological alterations come up with the depletion of osteoclastic giant cells, new bone formation and spindle cell proliferation. Such appearances are very much different from the histology of conventional GCTB and can be the reminiscent of osteosarcoma or malignancy in GCTB that actually leads to diagnostic difficulty to a greater extent [41].

Previous studies showed that multinucleated cells as well as several mononuclear cells expressed RANK all over GCTB. RANKL signaling in diseases like GCT is considered as an astonishing prototype in case of indicated translational research. Giant cell bone tumor treatment includes the curetteage irrespective of bone filler or adjuvants such as polymethylmethacrylate (PMMA) or phenol. In case of less possibility of surgical procedures, non-invasive methods for example; radiotherapy, radiofrequency thermal ablation, or chemoembolization, can be used. In some important cases in which surgery shows relatively minor functional impairment or some of the tumors expressing extensive local destruction, wide resection can be made available for such cases. However, resection may show a considerable morbidity [34].

Soft tissue recurrence in GCTB

In clinical practice, relapse in the soft tissue has been observed rarely in most of the cases as compared to local recurrence in bone. According to the latest reports, it has been shown that the soft tissue recurrence of GCTB often takes place in the area that is adjacent to curetteage site [55]. It may occur mostly with the help of contamination, when surgical removal of the tumor is performed. It has been reported that the reappearance chances of soft tissues in GCT are quite high post-surgery, in the range of 15–25% which goes up to 40–60%. Based on the category of the surgical methods being implemented, peripheral excision is related to an increased rate, while the spacious excision shows a decreased rate [42]. Tumor relapse has been commonly reported in the bone, at the site where the tumor was operated earlier and that this occurrence is depicted due to uninterrupted growth of the surplus tumor present in the bone. Soft tissue relapse irregularly manifests an outlying edge of ossification neighboring the mass, which is an idiiosyncratic, related to the soft tissue recurrence of GCTB. Radiographic and histologic findings of ossified soft tissue recurrence were reported in previous studies. In case of the need of early detection of the recurrence, MR imaging tool was suggested by Balke [56], that can be used for the purpose of any suspicious finding. In order to detect a suitable indicator for soft tissue recurrence of GCTB, peripheral rim of ossification surrounding the mass was shown to be a potential source. Some previous studies observed a low detection rate in ossification based on the plain radiography. Also, the proper recognition of the radiographic characteristics of soft tissue recurrence of GCTB have not been shown in previous studies, an accurate diagnosis and appropriate treatment could be facilitated with the help of in-depth studies [57].

The current advancement in radiological imaging has made it possible to detect small soft tissue abrasions with the help of sensitive modalities. The detection of soft tissue masses can be done with the help of MR imaging and it can be helpful to reveal the extent of the lesion, while there are chances that the outcome may be nonspecific. Ossification can be detected by plain radiography and CT scan because both the tools are sensitive enough in this case. A new classification was proposed regarding the soft tissue recurrence of GCTB and it is based on the integration of the plain radiograph and MR imaging [58]. A study was recently conducted in which 3 patients were identified and labelled accordingly as pure soft tissue recurrence without ossification (Type III), 2 as peripheral ossification (Type I) and the other one as central ossification (Type II). It was observed that ossification of soft tissue is occasionally identified in the central portion and usually at the periphery. Furthermore, it was also observed that there might be a recurrence lesion at high proportion irrespective of ossification in case of clinical practice. Plain radiography showed the suspicious soft tissue mass in the patients whereas, MR imaging was used to determine the recurrence of GCTB in the soft tissue. On the basis of requirement, some additional diagnostic studies, specifically a biopsy could be done with the help of computed tomography and it could be helpful to resolve the issue of soft tissue relapse [59].

Histopathological and radiological aspects in GCTB

According to the review literature, recently, a 16 year old male patient was observed in which a bony hard swelling involved the entire right side of face extending from malar region to lower border of mandible. Intra-oral examination showed that a well-defined inflammation expanded to a certain distance from the retro-molar region covering the soft tissue, the anterior ramus of mandible. The
Conclusion and Future Perspectives

Giant cell tumors can be eminently pleomorphic and some of them are seen ellipsoidal to round or spindle shaped. The prevalence of abundant osteoclast like giant cells containing large pleomorphic nuclei with irregular nuclear membrane was also observed and clearly apparent nucleoli were also cited in few cells and also the vesicular nuclei and diverse mitotic shapes were crystal clear in tumor cells. Also the space covered with lace like osteoid deposits encircling the tumor cells and bone destruction was also clearly visible. There was no occurrence of blood filled cystic spaces or vascular spaces reported in this case. Thus, it was proclaimed that histopathological process supports easy requirements to perform the straight forward diagnosis of giant cell rich osteosarcoma [62].

The radiological features of both osteosarcoma rich in giant cells and the conventional osteosarcoma are entirely different. The distinctive radiological uncovering of reappearance has been reported to be the contemporary domain for the destruction of bone at the excision extremity alongside the intra-lesional bone graft matter resorption taking place as per the continuous imaging analysis reports. Assessment methods in case of tumor relapse could be effectively determined with the help of comparison of further observation of the images with the preliminary paradigm autopsy illustration and deliberate investigation of the images. These findings resemble to benign or malignant giant cell tumor in most of the cases. They have been reported as osteolytic contusion in both head and neck region as well as in long bones [63]. A 3D CT scan was shown to come up with a large tumor lump along with tumor osteoid that forms a composite network emanating from the body, angle of mandible and involving whole of ramus and condylar neck. According to histopathological study, it is difficult to diagnose giant cell rich osteosarcoma (GRCO) because it has impending analogy to benign or malignant giant cell tumor. GRCO being an allying sarcoma with sparse formation of osteoids and a large amount of osteoclast-like giant cells shows an impressive resemblance to giant cell tumor. The possibility of diagnosis prevails due to the subsistence of osteoid formation by the tumor cells. A few osteoclast-like giant cells present in about 13–25% of cases of osteosarcoma are mostly observed in haemorrhagic and perivascular areas.

Conclusion and Future Perspectives

The general mechanism of the giant cells was reviewed with respect to their important role in the emergence of bone tumor. p63 expression contributes significantly towards the development of giant cell tumor. The p63 nuclear expression was witnessed in 96.8% of bone related giant cell tumor, 75.0% of brown tumors (cases of tenosynovial giant cell tumors were precluded), 14.3% of osteosarcomas, 22.2% of aneurysmal bone cysts, 68.7% of chondroblastoma cases, 50% of fibromas with non-ossifying state. Hence, p63 expression helps to a greater extent in dealing with the giant cell tumor in bone in its diagnosis and effective treatment. The H3F3A alterations such as: p.Gly35Trp, p.Gly35Leu, p.Gly35Val, p.Gly35met, p.Gly35Glu were observed in giant cell tumor with the help of point mutations. Thus, gene mutation analysis of different genes responsible for GCTB contributes effectively towards understanding the giant cell tumor in bone. In case of histopathological analysis, plain radiography and CT scan can be a potential source to notify ossification process in GCTB. These tools are highly precise in this case because of high chances of accuracy. The correct medical diagnosis, in which the mutations in the H3F3A gene are revealed in all the possible sections, is an expeditious as well as a sensitive analysis method that particularly takes giant cell rich sarcomas into consideration. This advanced gene mutation analysis tool plays an exceptional role in case of demarcation of GCT from tumors with conformity at histological level. RANKL reactivation process also plays an important role in developing the giant cell bone tumor.

This overview will help the researchers with the basic idea about GCTB and it will help to understand the development of giant cell tumor of bone with respect to the different factors such as; p63 gene expression, H3-3 histone mutations, RANKL. etc. With the help of this review study, it could be possible for the researchers to shift the focus towards highly advanced techniques to detect detailed information regarding many more putative and procurable prognostic biomarkers, predictive biomarkers as well as diagnostic biomarkers for GCTB as the need of the hour is to develop highly specific gene inhibition strategy as well as effective therapeutic techniques in order to discover and develop highly accurate treatment methods to control these types of bone tumors at global level.

References


