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REVIEW **Open Access**

Giant cell tumor of bone: An update, including spectrum of pathological features, pathogenesis, molecular profile and the differential diagnoses

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Summary. Giant cell tumor of bone (GCTB) is an enigmatic tumor. Despite its benign histological appearance and clinical behavior in most cases, it is associated with recurrences, uncommonly metastasis, and rarely with a malignant transformation. During the last few years, there has been a significant evolution in the diagnosis and management of GCTB, including discoveries related to the underlying pathogenesis (RANK/RANK/OPG pathway), with treatment-related implications in the form of denosumab (approved inhibitor for targeting RANKL), leading to improved surgical resections, especially in cases of recurrent, large and borderline resectable tumors. Lately, a specific Histone mutation, namely *H3.3G34W* underlying almost all GCTBs has been discovered, further leading to the identification of a highly sensitive and specific immunohistochemical antibody marker, H3.3G34W, which is very useful for an exact diagnosis of a GCTB, including its differentiation from its various mimics, which has significant implications. This review describes clinicopathological features of a GCTB, including its variable features, recent concepts, underlying pathogenesis, post-denosumab related changes and various entities that constitute its differential diagnosis, including their molecular signatures, with treatment-related implications.

Key words: Giant cell tumor of bone, RANK-RANKL, H3.3G34W, Denosumab

Introduction

According to the recent World Health Organization (WHO) classification of tumors of bone, a giant cell tumor of bone (GCTB) is an intermediate malignant neoplasm that is locally aggressive and rarely metastasizes. It comprises 4-5% of all the primary bone tumors and 20% of benign bone tumors (Flanagan et al., 2020).1 Its estimated incidence rate is 1.2-1.7 cases per 1 million individuals per year (Turcotte, 2006; Gupta et al., 2008; Jain et al., 2011; Sobti et al., 2016).

GCTB was first described in 1818 by Cooper (Cooper and Travers, 1818). Subsequently, its malignant potential and, local aggressivity were reported by Virchow (David, 1988), and Nélaton (1860), respectively.

Clinical features

A GCTB mostly occurs in the mature skeleton and typically arises from the epiphyseal end of a long bone and often extends up to the articular surface or the subchondral bone plate. The most common sites of occurrence of a GCTB are the distal end of the femur, the proximal end of the tibia, and the distal end of the radius. When a GCTB occurs in immature skeletal bone, which is relatively uncommon, it involves the metaphysis of the involved bone. A GCTB rarely occurs in the small bones, such as the metacarpals, metatarsals, or in the jaw bones (Dahlin et al., 1970; McGrath, 1972; Campidelli et al., 2007; Beebe-Dimmer et al., 2009). Within the vertebral column, GCTBs involve the cervical, thoracic and lumbar regions, as well as the sacrum, mostly the vertebral body. This tumor can occur at any age, but the most commonly affected age group is 20 years to 45 years (McGrath, 1972; Flanagan et al., 2020).

Multicentricity is rarely described, accounting for less than 1% of all cases of GCTBs. Multicentric GCTBs are classified as metachronous and synchronous, based on the duration between the two lesions. In the case that the second lesion is diagnosed within six months of the first lesson, it is considered synchronous. However, when the second lesion is diagnosed six months after the first lesion, it is termed metachronous (Peimer et al.,

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1980; Eckardt and Grogan, 1986; Hoch et al., 2006; Wirbel et al., 2013).

Malignant transformation in a GCTB is relatively uncommon. It is further classified as a primary malignant GCTB or secondary malignant GCTB. Primary malignant GCTB is a malignant tumor/sarcoma arising in a benign GCTB, whereas secondary malignant GCTB arises post-treatment, mostly after radiation therapy, in a previously diagnosed case of a benign GCTB (Dahlin et al., 1970; McGrath, 1972; Beebe-Dimmer et al., 2009).

Despite its benign nature, a GCTB has been known to metastasize. In 1926, Finch and Gleave (1926) discovered the first case of lung metastasis in a benign GCTB. The reported incidence of metastasis in a GCTB varies between 1% to 9% (Finch and Gleave, 1926; Viswanathan et al., 2010). The reported interval between a diagnosis of a primary GCTB and metastasis ranges from 0 to 10 years (an average of 3.5 years) (Gresen et al., 1973; Dominkus et al., 2006; Viswanathan et al., 2010). As such, there are no such predilection factors to predict metastasis (Gresen et al., 1973).

Radiological features

Radiological examination constitutes one of the first diagnostic modalities in the evaluation of a bone neoplasm, including a GCTB.

On a plain radiograph, a GCTB appears as a lytic lesion in the epiphyseal end of the long bone that might extend up to the metaphysis and the articular surface or the subchondral bone plate. Most GCTBs have a circumscribed border with a non-sclerotic margin, known as a geographic lesion. They do not display punctate calcifications, intralesional bone formation, or periosteal reaction, unless these are pre-treated with denosumab (Fig. 1) (Purohit and Pardiwala, 2007; Rekhi et al., 2017; van Langevelde, and McCarthy, 2020).

While a plain radiograph provides basic radiological details, computed tomography (CT) scan and magnetic resonance imaging (MRI) are important for staging and surgical planning (Hudson et al., 1984; Purohit and Pardiwala, 2007). A CT scan is useful in providing additional information, such as tumor extension into the extra-osseous portion and tumor relationship to the adjacent structures. Additionally, it can provide information regarding cortical integrity, thickness, and the presence or absence of matrix calcification. MRI is useful in identifying fluid-fluid levels, as a result of a secondary aneurysmal bone cyst (ABC) component, or due to intratumoral hemorrhage (Hudson et al., 1984; Resnik et al., 1986; Kaplan et al., 1987).

While radiological features provide a reasonable amount of information regarding the nature and the extent of the lesion, a biopsy is necessary for an exact diagnosis, including differentiating it from other giant cell-rich lesions/neoplasms (van der Heijden, et al., 2014).

Pathogenesis of GCTB: Bone morphogenesis, remodeling, and resorption are mainly controlled by osteoclasts; therefore, osteoclasts play a central role in these processes (Yasuda et al., 1998). The osteoclasts are differentiated from the hematopoietic cells, which are controlled by various members of the tumor necrosis factors (TNFs), such as osteoprotegerin (OPG), and OPG ligand/receptor activator of nuclear factor NF-κB (RANK) ligand / TRANCE. Stimulators for bone resorption include parathyroid hormone (PTH), prostaglandin E2 (PGE2), 1, 25-dihydroxy vitamin D3, interleukin (IL)-11, and IL-6 (Hsu et al., 1999; Huang et al., 2000; Morgan et al., 2005).

These simulators are classified into three categories, based on the mechanism by which they induce signals to osteoblast/stromal cells. These are via vitamin D receptor-mediated, protein kinase A-mediated signals (PTH and PGE2) and Gp130-mediated signals (IL-6 and IL-11). These stimulators induce RANK ligand / TRANCE / OPG ligand expression on the osteoblasts and stromal cells. Osteoprotegerin (OPG) is one of the negative regulators of osteoclastogenesis, while OPG ligand / RANKL / TRANCE plays a critical role in osteoclastogenesis by its ability to express genes involved in osteoclast differentiation. OPG ligand along with colony-stimulating factor-1 (CSF-1) and

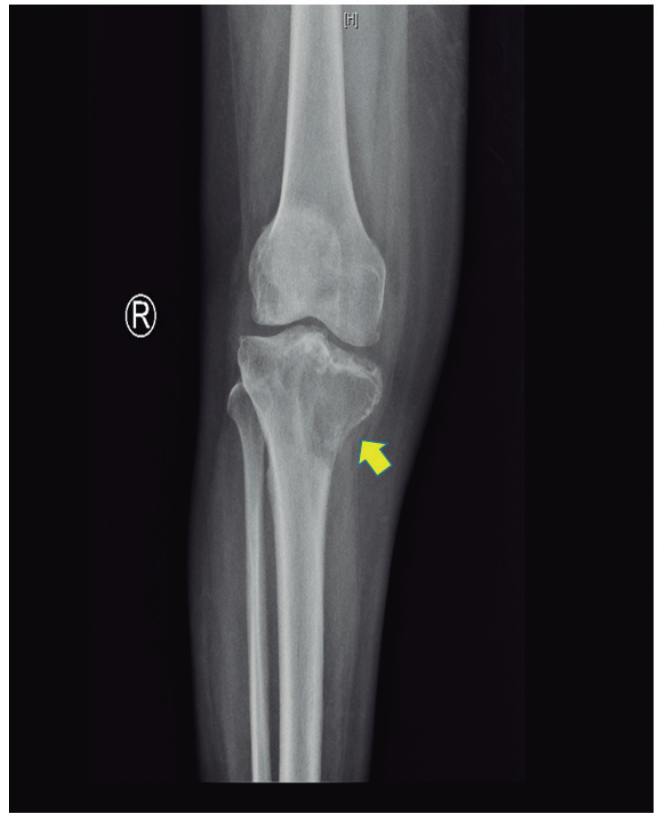

Fig. 1. Case of Giant cell tumor of bone (GCTB), showing a subarticular, well defined, expansile, lytic lesion in the upper end of tibia, associated with cortical thinning.

macrophage colony-stimulating factor take part in the process of osteoclast activation and bone maturation. OPGL is described as a ligand for the RANKL (RANK) receptor (Hsu et al., 1999; Huang et al., 2000; Yasuda et al., 1998). Hsu et al. (Hsu et al., 1999) identified that mRNA of the RANK receptor is expressed in the osteoclastic giant cell (OCGC). They described that various TNF receptor-associated factors (TRAF) adaptor proteins are associated with the intracytoplasmic tail of the RANK receptor and regulate expression. The N-terminal of these proteins is the ring finger/zinc finger domain and the conserved C-terminal is the TRAF domain. One of the domains of the intracytoplasmic tail of the RANK receptor is between amino acid residues 547 and 581 of the C-terminal region, which can interact with TRAF2 and TRAF5. Another domain of the intracytoplasmic tail of the RANK receptor is between 336 and 453 amino acid residues in the middle region and is responsible for the interaction with TRAF-6. Interaction with the TRAF-6 binding domain causes osteoclastogenesis. The role of other domains remains undefined (Yasuda et al., 1998).

OPG ligand/RANKL/TRANCE stimulate osteoclastogenesis by stimulation of NF-κB via TRAF-6 through the RANK receptor. Activated NF-κB enters the nucleus and expresses the genes for osteoclastogenesis. OPG inhibits osteoclastogenesis by interrupting the above bindings (Fig. 2). Noticeably, RANKL is essential for the survival of osteoclasts and plays a crucial role in the pathogenesis of GCTB.

Denosumab is a human monoclonal antibody against RANKL. Denosumab prevents the binding of RANKL to its receptor and suppresses the differentiation, activation, and functions of the osteoclast. Therefore, denosumab inhibits osteoclast-mediated bone destruction by inhibiting RANKL-mediated signaling. Overall, denosumab inhibits the recruitment of bystander osteoclasts (Morgan et al., 2005; Xu et al., 2013). This helps make a lesion more surgically amenable, especially in cases of large, destructive, recurrent GCTBs (Puri et al., 2019). However, the spindle cells and the cells in and around the immature bone in denosumab-treated GCTBs are immunohistochemically positive for H3.3G34W and consistently show *H3F3A* mutations. These findings indicate that viable neoplastic cells might be present even after denosumab treatment (Girolami et al., 2016; Lüke et al., 2017; Kato et al., 2018; Yamamoto et al., 2018).

Molecular profile of a GCTB

In recent years, there has been a breakthrough in the molecular and immunohistochemical profile of certain osteoclastic giant cell-rich tumors, especially GCTB and chondroblastoma.

In a previous study, Behjati et al. (2013) observed driver somatic mutation in *H3F3A* and *H3F3B*, defining a GCTB and chondroblastoma, respectively. Histone 3.3 encodes replication-independent histones, *H3F3A* and *H3F3B*, which reside on chromosomes number 1 and 17, respectively. In that study, the authors observed *H3F3A* somatic mutation in 49/53 (92.4%) cases of GCTB. Out

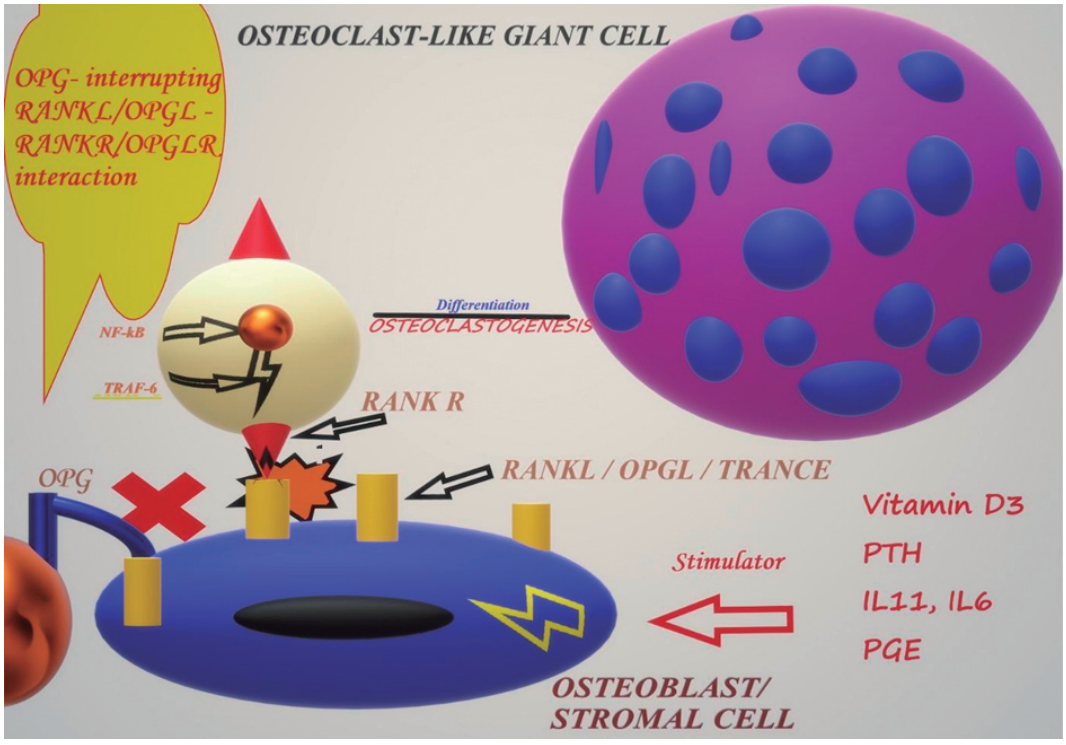

Fig. 2. Pathogenesis of Giant cell tumor of bone (GCTB).

of 49 cases displaying the mutation, 48 harbored p. *Gly34Trp* (*G34W*), while a single case harbored p. Gly34Leu alteration. In addition, the authors identified two cases of osteosarcoma (2/103, 2%), with the underlying p. *Gly34Arg* mutation.

Subsequently, Amary et al. (2017) reported H3F3A (H3.3) mutation involving substitution in glycine 34 in 96% of cases of GCTB. They observed p. *Gly34Trp* (*G34W*) mutation in 214/220 (97.3%) cases, and *G34L*, *V*, and *M* variants in the remaining 6/220 (2.7%) cases, displaying *H3F3A* mutations. In addition, they found *H3.3 p. G34R* mutation in 2/103 (~2%) cases of osteosarcoma. Subsequently, they tested cases for the immuno-histochemical expression of specific H3.3G34W in 3163 cases, including 235 cases of GCTB, including tumors occurring in various sites, such as long bones, sacrum, pelvis, axial bones, and small bones of the hands and feet. They observed positive staining in 213 (90.6%) cases of GCTB. Furthermore, on genotyping, they observed 6/22 negative cases harboring p. G34 V, L, and M substitution. Site-wise, they observed positive H3.3 G34W immunoexpression in 174 / 184 (94.5%) tumors occurring in the appendicular long bones, in all nine tumors occurring in the sacrum (9/9), in all 13 tumors in the pelvic bones, in 3/5 tumors occurring in the axial bones (excluding sacrum) and in 14/24 tumors occurring in the small bones. They also included 750 other tumors, including mimics of GCTB and 2,178 other neoplasms for evaluating the sensitivity and specificity of H3.3G34W immunostaining. They observed positive immunoexpression in 11/2928 (0.375%) tumors, including a single malignant GCTB, and in 10 osteosarcomas, mostly containing giant cells.

In a yet another study, Lüke et al. (2017) studied the immunohistochemical expression of H3.3G34W in 23 cases of GCTB that were *H3F3A* mutation-positive. They also studied the immunohistochemical expression of H3.3G34W in 36 giant cell-rich lesions, displaying wild-type *H3F3A*. These included brown tumors of hyperparathyroidism (n=1), ABC (n=6), chondroblastoma (n=6), NOF (n=5), fibrous dysplasia (n=2), tenosynovial giant cell tumor (n=9), giant cell-rich sarcoma (n=1) and osteosarcoma (n=6). They detected strong crisp nuclear staining in the mononuclear stromal cells of GCTB, ranging from 10 to 90% tumor cells in all cases (23/23, 100%). Out of 23 cases, two cases (recurrence of primary tumor and resection sample) showed a negative result for *H3F3A* mutation by Sanger sequencing, despite positive immunostaining in 10-40% tumor cells. They concluded that the reason for the negative sequencing result was a low number of neoplastic cells that were out-numbered by non-neoplastic cells. They also found a reduction of H3.3G34W positive tumor cells with replacement by fibroblast and strand-like osteoid in post-denosumab treated tumor sections, which were morphologically associated with a reduction of OCGC. None of the other giant cell-rich lesions (0/36) showed positive staining in that study. That study also revealed the utility of immunohistochemistry over Sanger sequencing in certain cases, such as post-denosumab treated specimens and small biopsy specimens comprising a small number of tumor cells. Given that all *H3F3A* positive samples showed significant positive immunohistochemical expression even after both acid-based and EDTA decalcification, immunohistochemistry seems to be one of the most reliable techniques for substantiating a diagnosis of GCTB.

Cleven et al. (2015) studied the association of H3K36me3-trimethylation staining and ATRX staining with *H3.3G34W/V* and *H3.3K36M* mutation in various giant cell-rich lesions such as GCTB, chondroblastoma, ABC, chondromyxoid fibroma (CMF) and telangiectatic osteosarcoma. They detected *H3F3Ap. G34* mutation in 41/ 69 (69%) cases of GCTB and *H3F3B p. K36M* mutation in 7/10 (70%) cases of chondroblastoma, using Sanger sequencing. They did not identify these mutations in any other giant cell-rich lesion/tumor that they tested for the same (100% specificity). In another study, Schaefer et al. (2018). detected positive H3.3 G 34W staining in 22/26 cases (85%) of GCTB, across various types of specimens. Furthermore, they found two cases of classical GCTB with wild-type *H3F3A* and two other cases harboring *p. G34* and *p. G34L* mutation, respectively. Additionally, they observed a diffusely positive staining pattern in half of the cases of malignant GCTB.

The specific *H3.3 H3F3A G34W* mutation is also reported in cases of recurrent GCTB and post-denosumab-treated residual GCTB. In a relatively recent study, Ud Din et al (Ud Din et al., 2020) observed a reduction in the number of OCGC in post-denosumab treated cases of GCT, along with a decreased immunohistochemical expression of H3.3 G34W in 19 cases of post-denosumab treated GCTBs. They attributed this reduced expression to the lower antigenicity of neoplastic mononuclear cells. Lately, Gong et al. (2021) reported positive H3.3 G34W immunostaining in 91.5% of cases of GCTB, including classical GCTB (164/180), recurrent GCTB (19/19), metastatic GCTB (5/5), adolescent GCTB (13/15), and malignant GCTB (4/5). They observed *H3F3A p. G34* mutation in 94.6% cases of GCTB , with *p. G34W* alteration (203/212) as the most common, followed by *G34L* alteration (4/212), *p. G34V* alteration (3/212) and *p. G34R* alteration (2/212).

Recently, Panagopoulos et al (Panagopoulos et al., 2022) reported that a subset of osteoclastic giant cell-rich tumors of bone display *HMGA2::NCOR2* fusion gene.

Pathological features

Gross features

The most commonly received specimens are curettage specimens that are quite voluminous, soft, and

brownish. On gross examination of a resection specimen, a GCTB appears as a well-defined and asymmetrically expanded neoplasm. The surrounding cortex might be thinned-out or destroyed. It is heterogeneous on the cut surface with a soft, friable, dark reddish appearance. Additionally, yellowish-white areas, corresponding to the fibrous tissue and areas of hemorrhage, including blood-filled cystic spaces, corresponding to the ABC-like changes, might be seen (Gupta et al., 2008; Flanagan et al., 2020)

Post-denosumab treated resection specimens reveal prominent solid and fleshy areas, with variably cystic areas, as a result of tumor response and prominent fibro-osseous proliferation (Rekhi et al., 2017).

Microscopic features

Histopathologically, a GCTB is composed of monotonous sheets of round to oval to spindle-shaped cells, macrophage-like mononuclear cells, and several osteoclastic giant cells (OCGC). The mononuclear stromal cells, which constitute the neoplastic/tumor cells, contain ill-defined cytoplasm, vesicular nuclear chromatin and discernible nucleoli. The spindled stromal cells are cytologically bland and morphologically indistinguishable from the macrophages and other cells, such as fibroblasts. There are several OCGC that are evenly distributed throughout the tumor and contain more than 50 nuclei, which are more than a typical osteoclast. The nuclei of the OCGC and stromal cells are mostly similar in appearance. Typical mitotic figures are invariably noted amidst the stromal cells. Venous involvement is frequently seen in a GCTB. However, this is not an indicator of malignancy (Mangham, 1999; Gupta et al., 2008; Flanagan et al., 2020).

Certain cases show variations in the classic morphology, including fibrosis, reactive bone formation, cystic degeneration, foamy histiocytes (fibrous-histiocytoma-like), secondary ABC-like changes, non-ossifying fibroma (NOF)- like areas, degenerate atypia /symplastic changes (pleomorphic nuclei with irregular nuclear membranes, hyperchromatic nuclei, smudgy chromatin, and intranuclear pseudo inclusions), post-treatment associated infarction necrosis, increased mitotic activity, the latter especially in recurrent GCTs and, rarely, chondroid differentiation (Al-Ibraheemi et al., 2016; Sarungbam et al., 2016).

Malignant features are uncommon in a typical GCTB. A primarily malignant GCTB is relatively uncommon, as compared to a malignant/sarcomatous transformation in a GCTB. The latter is characterized by the presence of a typical GCTB, either in an earlier biopsy sample or with a present sample, along with unequivocally malignant/pleomorphic cells, often associated with atypical mitotic figures that are indicative of aneuploidy. A malignant transformation in a GCTB is considered as a dedifferentiated form of a GCTB that might display a component of osteosarcoma,

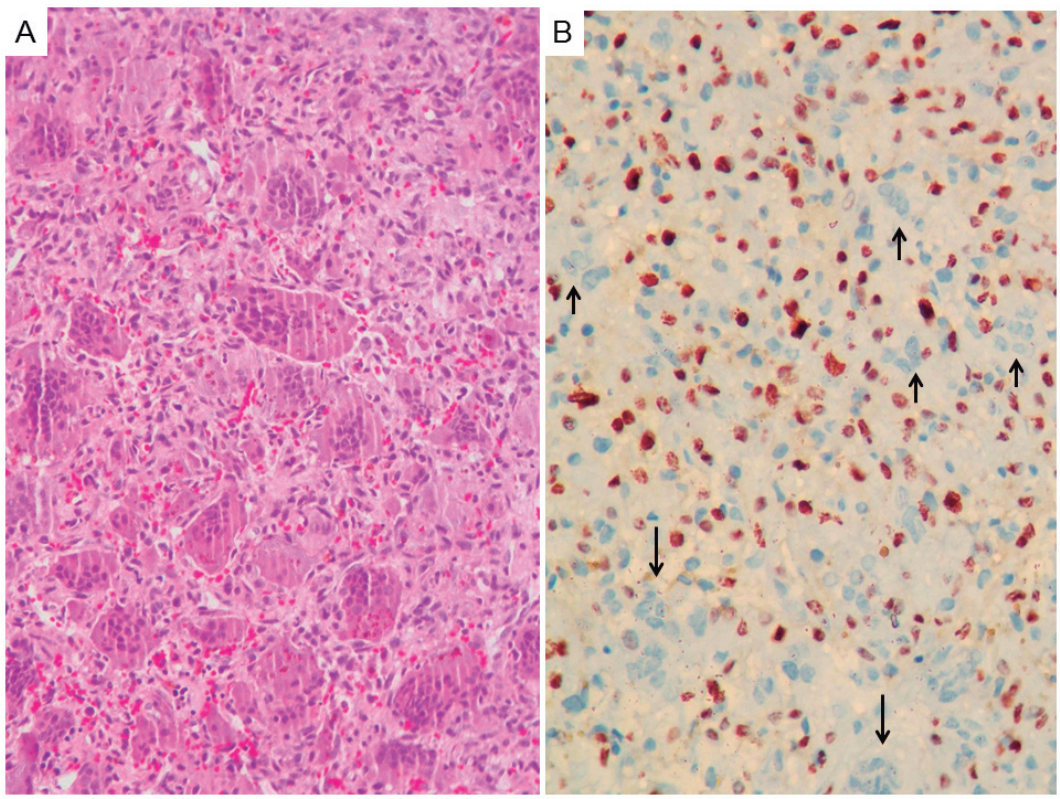

Fig. 3. A. Classical GCTB characterised by uniformly dispersed osteoclastic giant cells (OCGC) and intervening stromal, tumor cells. H and E. **B.** Diffuse, crisp, intranuclear, intense staining for H3.3 G34W in the tumor cells, and negative staining in the interspersed OCGC (arrows). Diaminobenzidine (DAB), A, x 200; B, x 400.

fibrosarcoma or a pleomorphic undifferentiated sarcoma (Meis, et al., 1989; Gong et al., 2012).

Importantly, post-denosumab treated specimens show a variable amount of reduction in the number of OCGC and replacement by conspicuous fibro-osseous proliferation, including reactive woven bone or osteoid formation in most of those cases. The other morphological features indicative of response are stromal hyalinization, fibrosis, hemorrhage, chronic inflammation, fibroblastic proliferation, and dystrophic calcification. A prominent woven bone formation mimics low-grade osteosarcoma. Therefore, a clinical history of treatment with denosumab is crucial to avoid a misdiagnosis of osteosarcoma (Branstetter et al., 2012; Rekhi et al., 2017).

Differential diagnoses and dilemmas

Various giant cell-rich lesions, including tumors that constitute differential diagnoses of a GCTB, are aneurysmal bone cyst (ABC), telangiectatic (giant cell-rich) osteosarcoma, giant cell granuloma, chondroblastoma, chondromyxoid fibroma (CMF), non-ossifying fibroma (NOF), osteoblastoma, tenosynovial giant cell tumor (TGCT), phosphaturic mesenchymal tumor (PMT) and brown tumor of hyperparathyroidism.

While various giant cell-rich lesions have certain distinct morphological features, there is a significant amount of histopathological overlap seen in these lesions. Certain features such as uniformly distributed OCGC, and monotonous sheets of round to spindle stromal cells, are useful to identify most cases of GCTB. However, few cases of GCTB show secondary changes, such as ABC-like areas, NOF-like areas, cystic degenerations, and reactive osteoid formation, which creates a diagnostic difficulty in differentiating this tumor from the corresponding mimic, especially on limited biopsy material (Al-Ibraheemi et al., 2016;

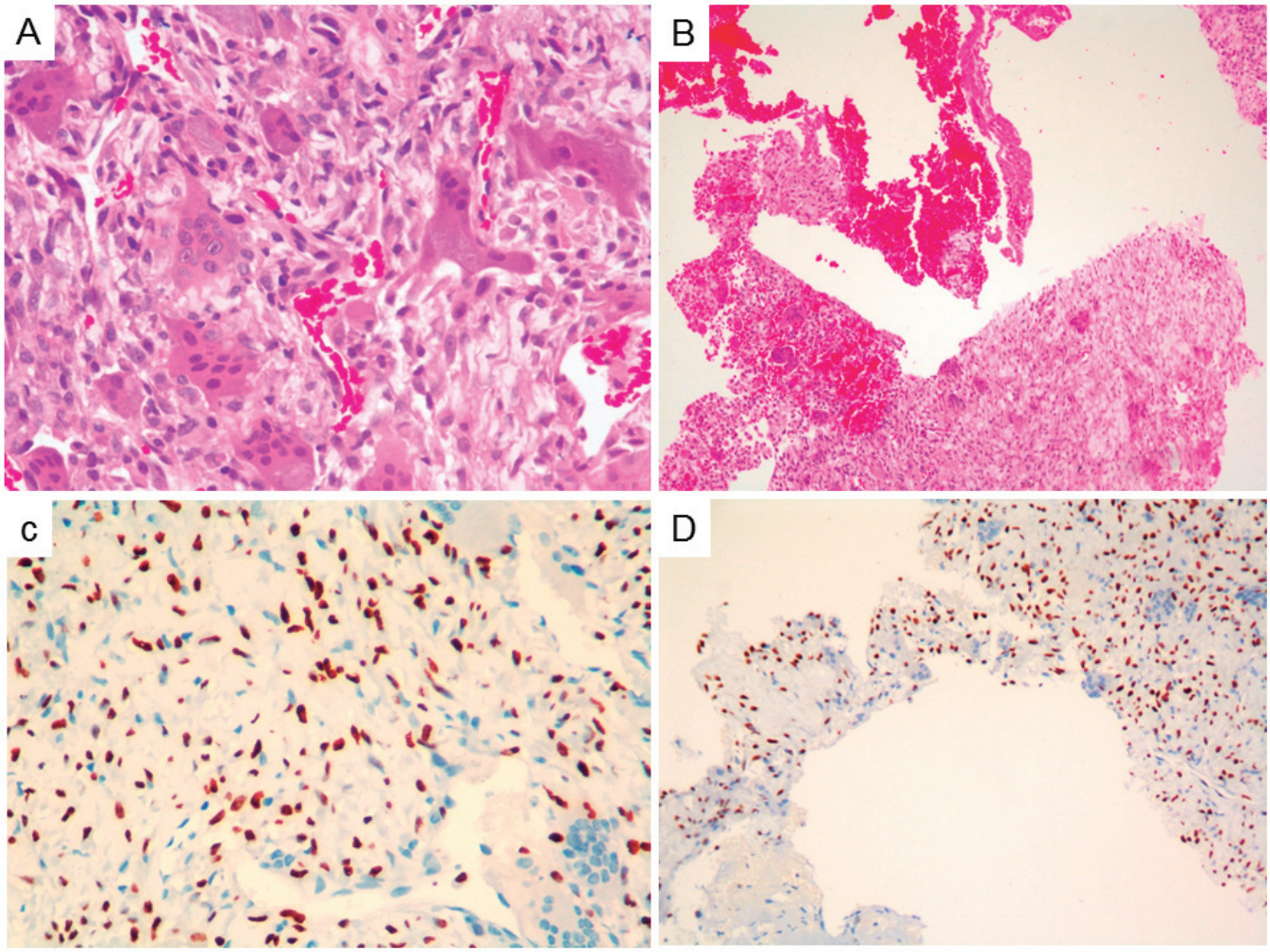

Fig. 4. Case of Giant cell tumor of bone involving sacrum. **A.** Classical areas of GCTB. H and E. **B.** Areas of secondary aneurysmal bone cyst (ABC). H and E. **C.** Diffuse and intense H3.3 G34W immunostaining. DAB. **D.** H3.3 G34W immunostaining in the areas resembling ABC. DAB, A, C x 400, B, x 20; D, x 200.

Rehkämper et al., 2018). It is crucial to make this distinction, given the associated treatment-related implications. A malignant GCTB invariably shows atypical stromal mitosis (Sarungbam et al., 2016).

Among various giant cell-rich lesions/tumors, there can be a diagnostic challenge in differentiating a GCTB from an ABC, GCTB from a chondroblastoma, GCTB from a giant cell-rich osteosarcoma and a GCTB from a giant cell reparative granuloma. Moreover, there can be a challenge in evaluating residual tumor cells in a case of post-denosumab treated resection specimen of a GCTB.

Given the fact that all these giant cell-rich lesions are treated distinctly, it is very important to differentiate and accurately diagnose these on a biopsy.

Chondroblastoma: A chondroblastoma is an epiphyseal (subchondral) tumor and histologically comprises immature chondrocyte (chondroblast), a variable number of OCGC, along with amphophilic to eosinophilic material/ "pink cartilage" (chondroid differentiation). These immature chondrocytes are dyscohesive mononuclear cells with small grooved nuclei. In addition, a pericellular "chicken wire-like" calcification is a characteristic diagnostic clue, but not identifiable in all tumors, especially on limited biopsy material (Akpalo et al., 2012; Cleven et al., 2016; Rehkämper et al., 2018). Immunohistochemically, DOG1 and H3.3 K36M constitute fairly sensitive and specific markers for reinforcing a diagnosis of chondroblastoma (Akpalo et al., 2012; Amary et al., 2016; Cleven et al., 2016; Schaefer et al., 2018; Rekhi et al., 2020).

Table 1. Immunohistochemical antibody markers for the diagnosis of various giant cell- rich tumors.

	Giant cell-rich Tumors	Immunohistochemical markers
1	Giant cell tumor of bone	P63 (Yamada et al., 2018) , H3.3AG34W (Highly sensitive and specific) (Amary et al., 2017; Lüke et al., 2017; Schaefer et al., 2018; Gong et al., 2021)
2	Chondroblastoma	S100 P, DOG1(33.3% to 100% sensitivity (Cleven et al., 2016; Righi et al., 2017) , H3.3K36M (Highly sensitive and specific) (Amary et al., 2016; Schaefer et al., 2018)
3	Osteoma and Osteoblastoma	FOS (73-100%% in osteoid osteoma and 57%-83% in osteoblastoma, invariably diffuse), (Amary et al., 2019; Lam et al., 2020)
4	Telangiectatic (Giant cell-rich) osteosarcoma	SATB2 (sensitive, but not specific) (Angelini et al., 2016)

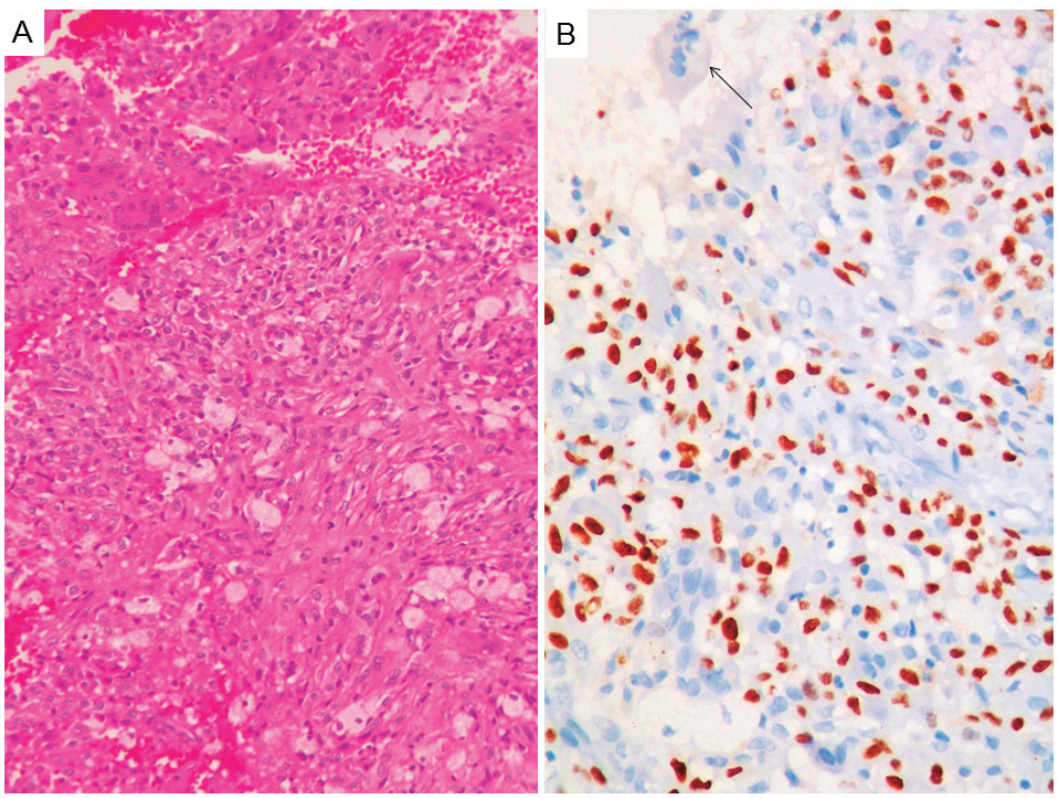

Fig. 5. Case of giant cell tumor of bone with fibrous histiocytoma-like areas. **A.** Several pale staining foamy histiocytes admixed with stromal mononuclear tumor cells with scattered osteoclastic giant cells. H and E. **B.** Diffuse H3.3 G34W highlighting the tumor cells and negative staining in the fibroblasts, histiocytes and the multinucleate OCGC (arrow). DAB. x 400.

Aneurysmal bone cyst (ABC)

ABC invariably involves the metaphysis and occurs in patients less than 20 years of age. Histopathologically, conventional ABCs are well-circumscribed and comprise multiple cystic spaces, separated by fibrous septa, showing predominantly fibroblastic proliferation, admixed with unevenly distributed OCGC, which might be more densely concentrated in the lining, adjacent to the areas of hemorrhage. Mitotic figures might be present, but an atypical mitotic figure is always absent. At places, reactive osteoid with surrounding osteoblastic rimming may be present, including "blue bone" formation or

Table 2. Various giant cell-rich tumors and their corresponding molecular signatures.

	Giant cell-rich lesion	Molecular alteration
1	Giant cell tumor of bone (GCTB)	H3F3A G34W/L/M/V (Amary et al., 2017; Lüke et al., 2017; Gong et al., 2021)
2	Chondroblastoma	H3F3B K36M (Behjati et al., 2013; Cleven et al., 2015)
3	Osteoma and osteoblastoma	FOS rearrangement (Lam et al., 2020)
4	Chondromyxoid fibroma (CMF)	GRM1 rearrangement (Nord et al., 2014)
5	Non-ossifying fibroma (NOF)	Hotspot KRAS, FGFR1 and NF1 (Baumhoer et al., 2019)
6	Phosphaturic mesenchymal tumor (PMT)	FN1-FGFR1, FN-FGF1 gene Fusions, FGF23 Overexpression(Lee et al., 2016)
7	Aneurysmal bone cyst (ABC)	USP6 gene rearrangement (Oliveira et al., 2004), CDH11-USP6 gene fusion (Sukov et al., 2008).

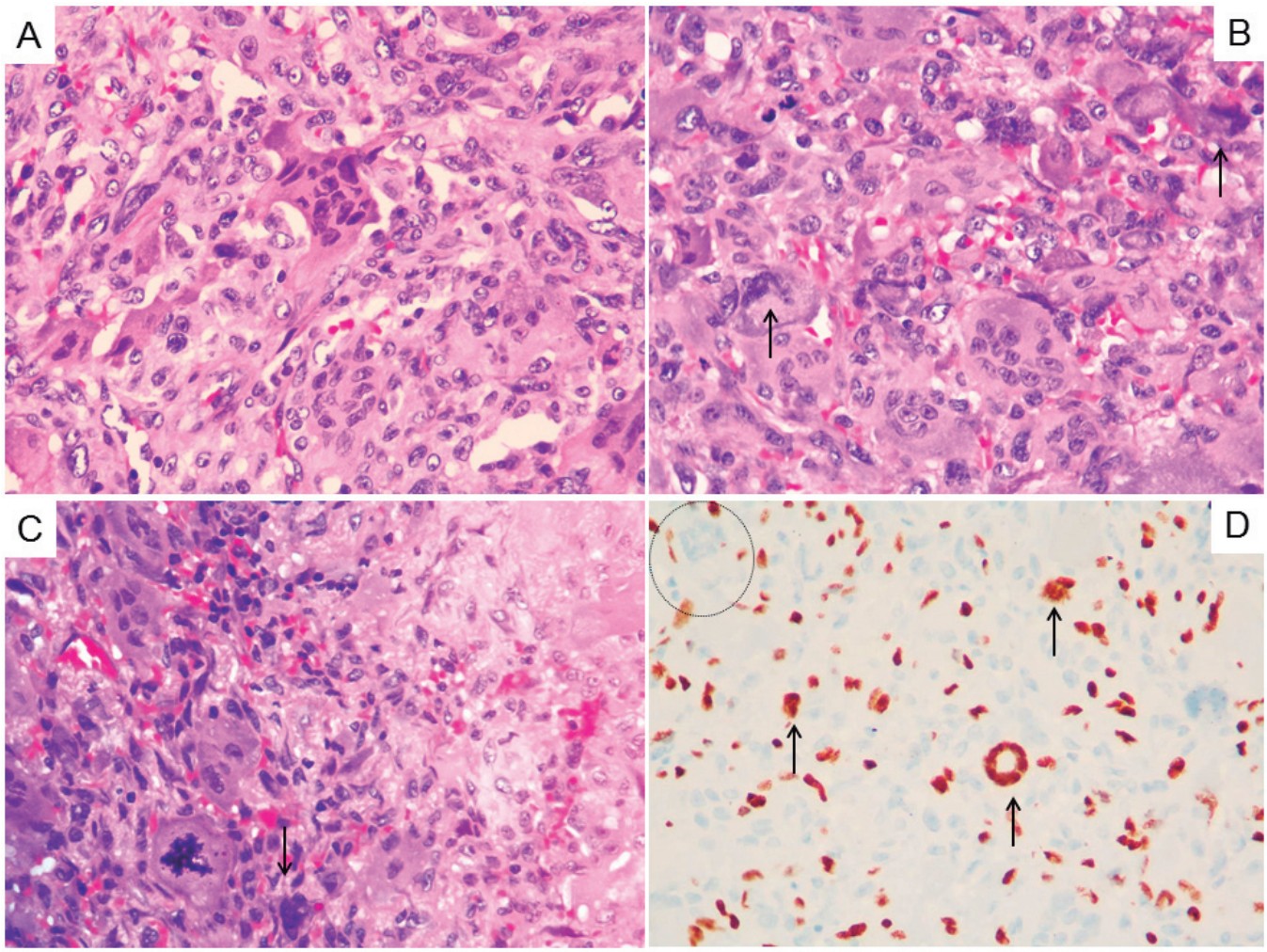

Fig. 6. Malignant giant cell tumor of bone (GCTB). **A.** Classic areas of GCTB. H and E**. B.** GCTB with stromal mitosis and scattered pleomorphic cells (arrows). H and E**. C.** Unequivocally pleomorphic cells and atypical mitotic figure. H and E.**. D.** Diffuse, intense H3.3 G34W immunostaining within the tumor cells, including the pleomorphic forms, negative staining in theOCGC (circle). DAB. x 400.

"chondroid aura".

A solid ABC is composed of moderately cellular, bland fibroblastic cells, arranged in a storiform pattern with unevenly distributed clusters of OCGC, areas of chunky calcification, parallel to the cyst wall, reactive bone formation, lined by osteoblasts and hemosiderin pigment-laden macrophages. (Mangham, 1999; Oliveira et al., 2004; Sukov et al., 2008; Agaram et al., 2014; Bahk and Mirra, 2015).

Telangiectatic osteosarcoma /giant cell-rich osteosarcoma: It is a metaphyseal tumor composed of fibrous walls surrounding blood-filled cystic spaces, admixed with scattered OCGC. However, tumor cells within the fibrous walls show marked nuclear pleomorphism/frankly malignant cells, and atypical mitotic figures, unlike a GCTB. A malignant osteoid formation may be noted (Sangle and Layfield, 2012; Angelini et al., 2016; Chow, 2016; Faisham et al., 2017).

Osteoblastoma

It is composed of predominantly bone-forming osteoblasts with haphazardly arranged woven bone, surrounded by osteoblastic rimming, in a loose fibrovascular stroma. Osteoblasts invariably align around the bone in a single layer, and the stroma is otherwise low in cellularity. OCGC might be scattered throughout the lesion. Atypical mitoses are always absent (Lichtenstein, 1956; Byers, 1968; Bertoni et al., 1993).

Chondromyxoid fibroma (CMF)

A CMF occurs in the metaphysis and is histopathologically composed of lobules of variably cellular chondromyxoid matrix , stellate to spindle-shaped cells and mature hyaline cartilage in the center of the lobules. OCGC are seen around the edge of the

Table 3. Sensitivity and specificity of immunohistochemical expression of H3.3 G34W in giant cell tumor of bone (GCTB), across various studies.

Sr. no.	Study	Year	Sample size	Sensitivity	Specificity
1	Amary et al., 2017	2017	n=3163	90.6%	99.7%
2	Lüke et al., 2017	2017	n=59	100%	100%
3	Schaefer et al., 2018	2018	n=55	85%	100%
4	Gong et al., 2021	2021	n=366	91.5%	100%

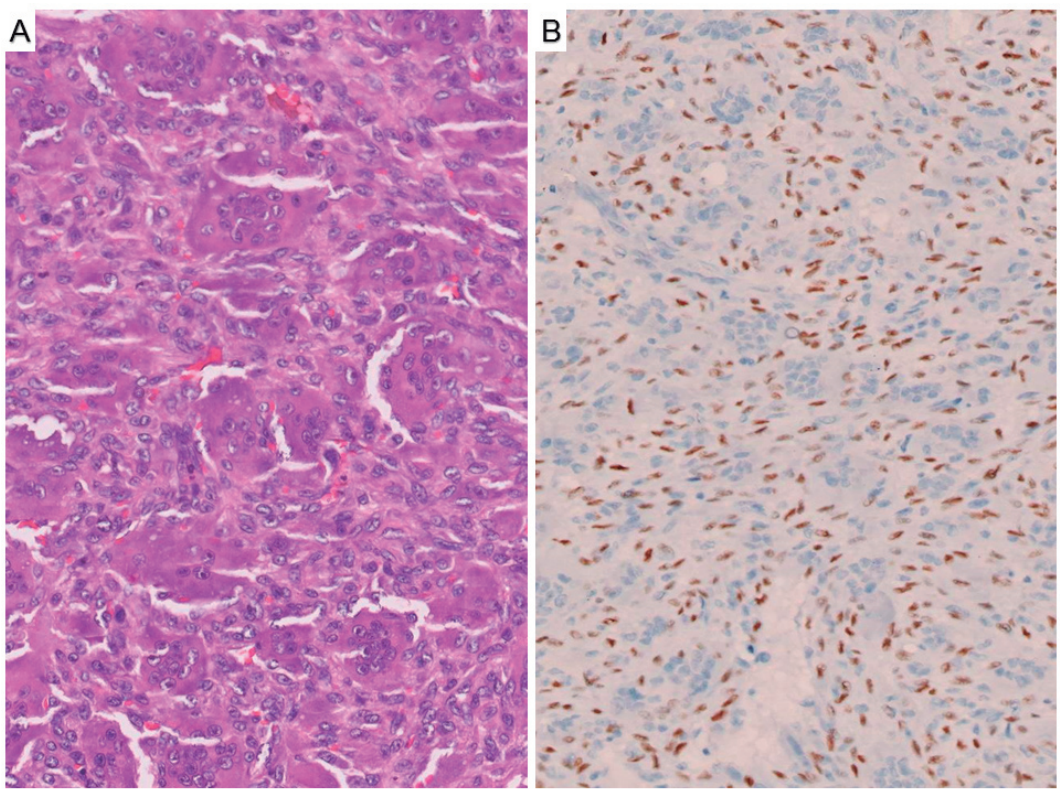

Fig. 7. A. Pre-denosumab treated GCTB, displaying uniform sprinkling of osteoclastic giant cells (OCGC). H and E. **B.** Diffuse, intense H3.3 G34W immunostaining in the tumor cells and negative staining in the OCGC. DAB. A, B, x 400.

tumor lobules. The tumor cells typically have a moderate amount of eosinophilic cytoplasm, and have ovoid to reniform nuclei. Towards the center of the lobules, the tumor cells are more spindle-shaped to stellate, while at the periphery they appear more epithelioid and chondroblast-like. Mature hyaline cartilage is rarely seen in a CMF (Jaffe and Lichtenstein, 1948; Rahimi et al., 1972; Wu et al., 1998).

Non ossifying fibroma (NOF)

A NOF mostly occurs in the metaphysis of immature skeletal bones and is histologically composed of plump spindle-shaped cells, lacking significant atypia, arranged in a typical storiform growth pattern with interspersed OCGC and variable amounts of reactive bone formation, along with pigmented and foamy histiocytes (Baumhoer et al., 2019).

Phosphaturic mesenchymal tumor (PMT)

A PMT is histopathologically composed of bland-appearing, round to spindled fibroblastic cells, arranged in sheets within a hyalinized or chondromyxoid matrix.

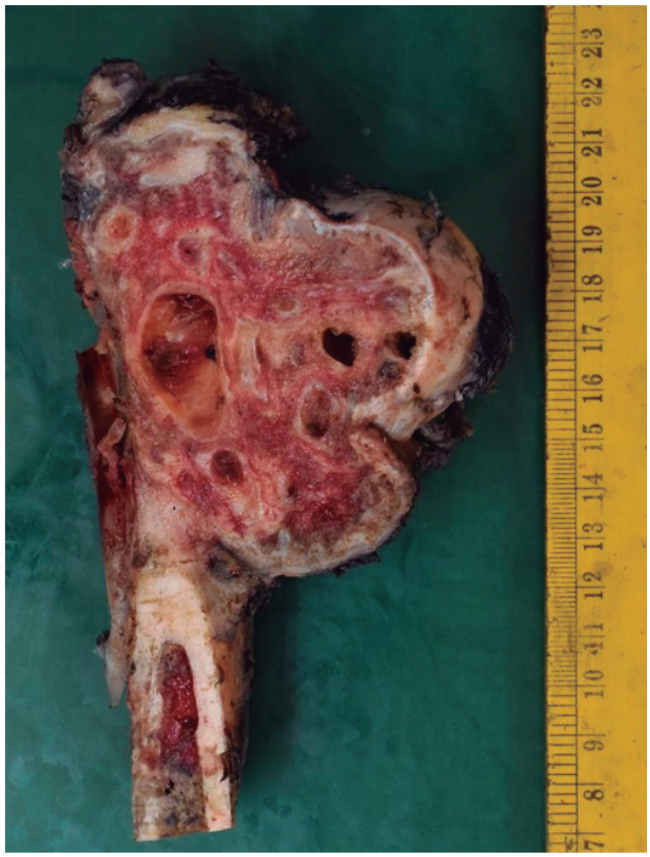

Fig. 8. Post-denosumab treated resection specimen, in a case of giant cell tumor of the bone, involving the proximal femur, showing a firm to hard cut surface (grey-white to pink) with few cystic areas(treatment response)

In addition, there are clusters of OCGC, microcystic changes, hemangiopericytoma-like arrangement of blood vessels, poorly formed cartilage or woven bone, and a characteristic "grungy calcification" (Bahrami et al., 2009; Agaimy et al., 2017; Yamada et al., 2018).

Rarely, a metastatic carcinoma, rich in OCGC can constitute a differential diagnosis. In such cases, epithelial markers, such as epithelial membrane antigen (EMA) and pan-cytokeratin (AE1/AE3) can be useful (Mangham, 1999).

A summary of the supportive immunohistochemical markers and molecular profile of various giant cell-rich lesions that can be utilized in cases of diagnostic dilemmas is listed in Table 1 and Table 2. The observed sensitivity and specificity of H3.3G34W immuno-staining across all the documented studies are listed in Table 3.

Diagnostic utility of immunohistochemical staining for H3.3 G34W

H3.3 G34W immunostaining is useful in differentiating a GCTB containing a secondary ABC from a primary ABC, chondroblastoma, NOF, giant cell granuloma, PMT, brown tumor of hyperparathyroidism, and a giant cell-rich osteosarcoma. Its diagnostic sensitivity ranges from 85%-100% and specificity ranges from 99.7%-100%, across various studies (Amary et al., 2017; Lüke et al., 2017; Schaefer et al., 2018; Gong et al., 2021). In this way, H3.3G34W is a highly sensitive and specific immunohistochemical marker for diagnosis of a GCTB, including in pediatric patients (Ambrosi et al., 2021). However, it cannot differentiate a benign from a malignant GCTB, given that both tumors display diffuse immunostaining. Most authors have reported retained immunohistochemical expression of H3.3G34W in the malignant component of GCTB, whereas others have reported loss of its immunoexpression in the malignant component (Amary et al., 2017; Righi et al., 2017; Tsukamoto et al., 2018; Yoshida et al., 2019). (Figs. 3-10). In a recent study, the authors reported a possible association with TP53 mutation and dysfunction of histone methylation in the form of loss of H3K27 trimethylation in the malignant progression of a GCTB. They observed 7/9 cases of malignant GCTB showing H3.3G34W immunostaining and the remaining 2 tumors displaying loss of H3.3G34W in the malignant component, along with heterozygous loss of *H3F3K* (Ishihara et al., 2022).

This has been useful to reinforce the present understanding that fibrous histiocytoma in bone represents a heterogeneous group of lesions, rather than a distinct tumor entity. Most of those tumors are GCTBs. Accordingly; fibrous histiocytoma of bone is no longer a distinct entity in the recent WHO classification (Flanagan et al., 2020).

H3.3G34W positivity in some cases of bone sarcomas without a component of GCTB seems to create debate in their diagnosis. It is possible that such tumours share

proximity with a malignant GCTB, especially when they occur in the epiphysis (Amary et al., 2017).

Treatment and related implications

Invariably, GCTBs are treated with curettage and/ or surgical resection, depending on the disease-extent. Following curettage, 15-30% patients develop tumor recurrences, depending on the thoroughness of the curettage procedure and the type of adjuvant therapy offered. Tumor recurrence is mostly seen within 2 years (Athanasou et al., 2013). In an earlier study of 470 GCTBs, there was a recurrence rate of 36.1%, and incidence of metastasis with these tumors was found to be 5.1%, including rare cases with multicentric disease (Gupta et al., 2008).

In view of the associated treatment-related implications, it is essential to differentiate GCTB from its various differentials. For example, minimally invasive treatment, including arterial embolization and sclerotherapy is considered in the management of certain cases of ABC, while radiofrequency ablation is considered as a treatment option for small-sized chondroblastomas, apart from curettage, in most cases (Rybak et al., 2009; Cottalorda et al., 2022). Denosumab is considered in certain cases of GCTB (recurrent, large-sized with thinned out peripheral rim), in order to convert those cases into more surgically amenable tumors (Puri et al., 2019).

To summarize, GCTB has evolved in a significant way in terms of its diagnosis, pathogenesis and the underlying molecular pathology. The molecular discoveries in the form of identifying specific underlying genetic signatures of the various giant cell-rich tumors, leading to the development of corresponding immuno-histochemical markers in certain tumors, have made a significant impact in differentiating a GCTB from its mimics. A diagnosis of GCTB can be formed on a

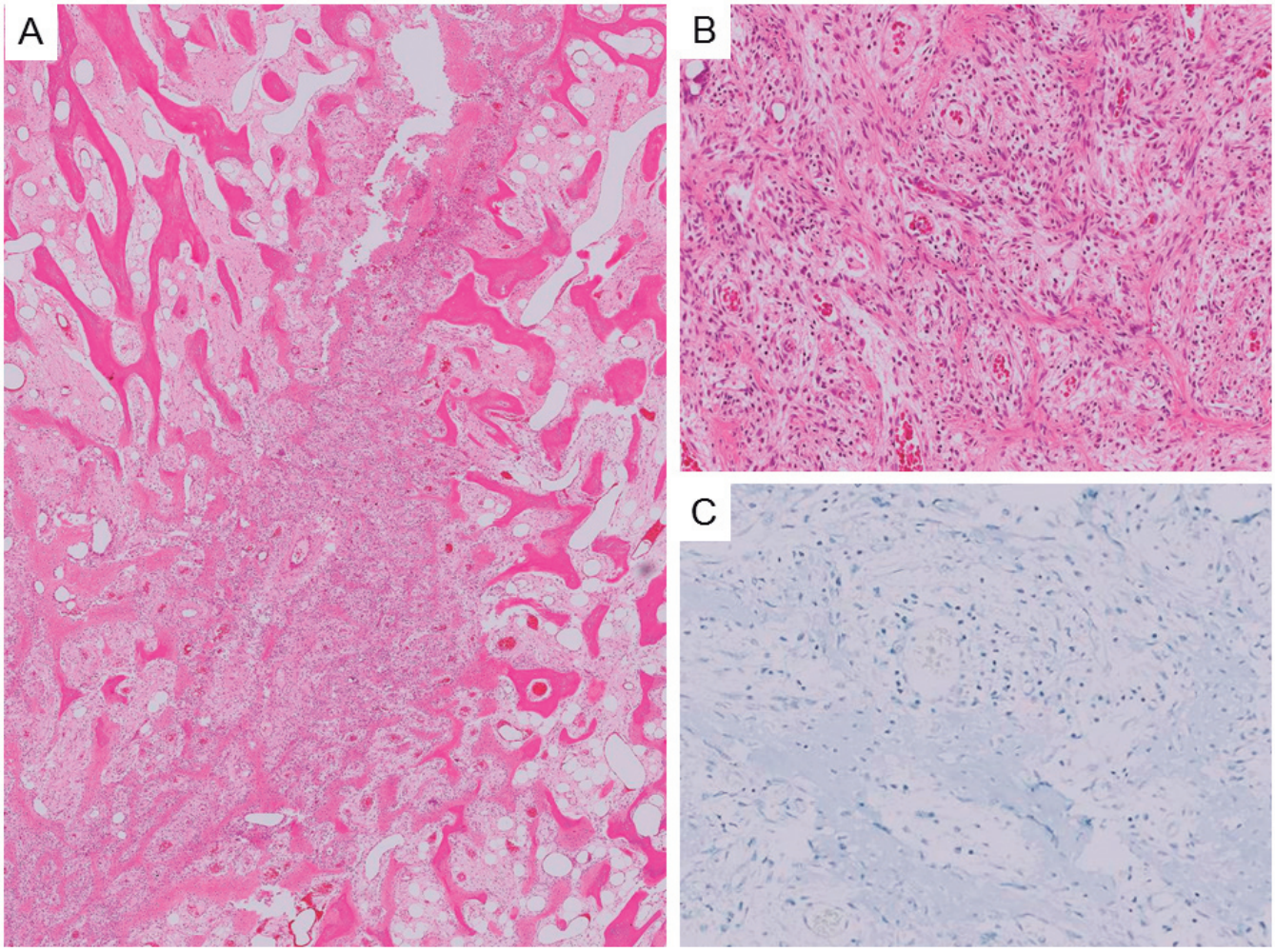

Fig. 9. A. Post-denosumab treated GCTB. Prominent woven bone formation, simulating a low-grade osteosarcoma. H and E. **B.** Fibroblastic cells and granulation tissue. H and E. **C.** Negative H3.3 G34W immunostaining (unusual). DAB. A, C, x 200; B, x 400.

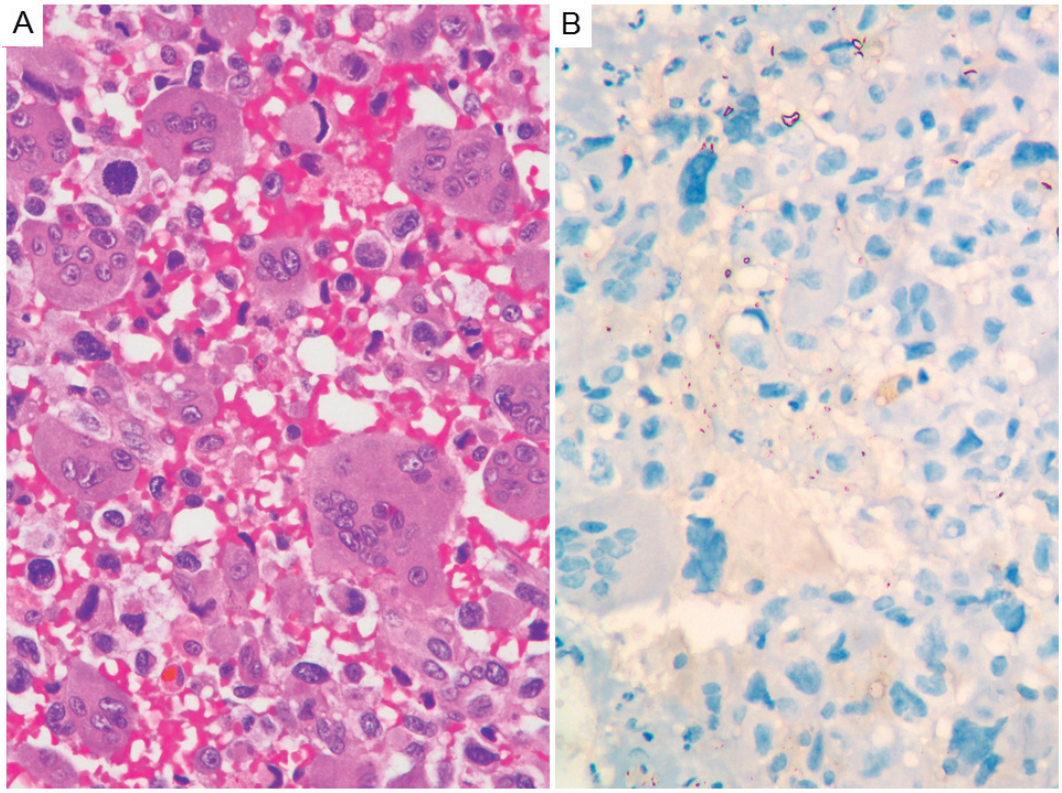

Fig. 10. A. Giant cell rich osteosarcoma. H and E. **B.** Negative H3.3 G34W staining. DAB. A, B, x 400.

routine microscopic assessment in a typical clinicoradiological setting. However, it would be optimal to include the results of H3.3 G34W immunohistochemical staining and/ or *H3.3 G34W* mutation, especially in cases of GCTB with overlapping clinical, radiological and pathological features with its other differential diagnoses. An exact diagnosis in all those cases has significant treatment-related implications, especially in present times, when conservative treatment approaches are being increasingly considered in certain giant cell rich lesions/tumors, except in cases of giant cell rich osteosarcoma.

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Conflict of interest of authors. None.

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