

GIANT CELL TUMOR OF BONE

Definition.

First described by Jaffe et al.¹, giant cell tumor of bone is a locally aggressive primary neoplasm of bone that is composed of proliferation of bland looking oval to polyhedral mononuclear cells, admixed with evenly distributed, osteoclast-type giant cells. The tumor is typically located with the epiphysis of long tubular bones or the epiphyseal equivalent in other bones²⁻⁴. In the most current WHO classification of bone tumors, giant cell tumor of bone is classified as a locally aggressive, rarely metastasizing neoplasm³.

General features.

Accounts for approximately 6% of primary bone tumors and 20% of benign bone tumors⁵. Previously, it was believed that the giant cells were formed by the fusion of the mononuclear neoplastic cells and it was assumed that the giant cells might also be neoplastic. Currently, giant cell tumor of bone is considered a neoplastic process derived from mononuclear cells exhibiting osteoblastic phenotype that express RANK-ligand (RANKL), which induces the formation of the osteoclast-type giant cells, from which the tumor derives its name. Most giant cell tumors of bone arise de-novo but can also arise in bones affected by Paget disease of bone.

Clinical features.

Most patients are skeletally mature at the time of diagnosis (usually between the age of 20-40 years); it rarely arises in skeletally immature individuals; less than 10% arise in patients under the age of 18 years⁶. Females are affected more common than males. It is more common in the Chinese population accounting for approximately 20% of primary bone tumors⁷. Patients usually complain of pain and swelling that may or may not be associated with a pathologic fracture. When the tumor involves the sacrum, the presenting symptom is usually that of long standing lower back pain or neurologic symptoms. The clear majority of tumors are solitary, but around 1% of patients present with multiple synchronous or metachronous lesions⁸.

Sites.

Most tumors arise at the ends (epiphyses) of long tubular bones; the most common location being the distal femur, proximal tibia and distal radius. The pelvis and sacrum are the most common locations within the axial skeleton; it is uncommon for giant cell tumor to arise in other vertebrae – when it does it usually involves the vertebral body, sometimes with extension into the posterior elements; a tumor confined to the posterior elements only is not a giant cell tumor of bone and more likely is an aneurysmal bone cyst or an osteoblastoma. A variety of other bones/locations can be affected including the greater trochanter, patella and hyoid bone⁵. It is rare for a giant cell tumor of bone to arise in the craniofacial skeleton except in the setting of pre-existing Paget disease of bone. Giant cell tumor of the small bones is rare.

Radiographic Features.

The radiographic features of giant cell tumor of bone, when arising in a typical location such as long tubular bones, is quite characteristic and in most cases diagnostic. When arising in an extra-epiphyseal location, the radiographic diagnosis can be more challenging and non-diagnostic. The typical giant cell tumor of bone is intramedullary and lytic. When involving long tubular bone it usually involves the epiphysis, metaphysis and if large may extend into the diaphysis. The tumor typically extends to the subchondral bone plate although a small rim of

bone may separate the tumor from the overlying articular cartilage. The margins are well-defined but may be moth-eaten. Surrounding sclerosis is uncommon. Large tumors may expand the bone, elevate the periosteum and extend into the surrounding soft tissues. When cystic, fluid-fluid levels, as seen in aneurysmal bone cyst are seen. Occasionally the giant cell tumor can show a more trabecular pattern radiographically and this appears to correlate with extensive fibrohistiocytic features⁴. Pathologic fracture may be present. Campanacci⁹ came up with a grading system based on the radiographic appearance of the tumor. *Grade 1 (calm type)* tumor is well-defined with a thin rim of bone; *grade 2 (active type)* tumor lacks a radiopaque rim and *grade 3 (aggressive type)* tumor has ill-defined borders. This grading system, however, has not been shown to correlate with clinical behavior. Rarely does the tumor not involve the epiphysis and may be confined to the metaphysis or the diaphysis; this is usually seen in giant cell tumor of bone occurring in skeletally immature individuals⁶. On CT scan the tumor is lytic and well-defined. Magnetic resonance imaging (MRI) shows no specific features but is helpful in identifying the intramedullary and extraosseous extension of the tumor. When giant cell tumor of bone locally recurs in the soft tissues it typically produces a shell of reactive bone at the periphery. Similar reactive bone formation can also be seen in lung metastases. After denosumab therapy the tumor displays increased sclerosis that starts at the periphery of the tumor and with time extends towards its center.

Gross Findings.

Giant cell tumor of bone is red brown, friable and hemorrhagic. It may contain grayish or yellow areas. It is usually predominantly solid but can have cystic areas (secondary aneurysmal bone cyst-like changes). It may expand the bone, break through the cortex and involve the adjacent soft tissues. After treatment with denosumab the tumor has a gray, yellow and solid cut surface^{10,11}.

Microscopic Findings.

Giant cell tumor of bone is composed of an admixture of mononuclear cells and multinucleated osteoclast-like giant cells. The mononuclear cells are oval to plump to slightly spindle shaped with central nuclei that are very similar in morphology to the nuclei of the osteoclast-type giant cells. The cytoplasm is scant and eosinophilic. There are at least two types of mononuclear cells; mesenchymally derived cells with osteoblastic phenotype (that express RANKL) and mononuclear osteoclast precursors (that express RANK). The mononuclear cells can be mitotically active although atypical mitotic figures are not seen. The multinucleated osteoclast-type giant cells are evenly distributed throughout the tumor and have numerous (50-100) nuclei that are clustered within the center of the cell. The nuclei have a finely dispersed chromatin pattern and small purple nucleoli. Mitotic figures are not seen in the osteoclast-type giant cells. In other areas, the tumor can demonstrate a benign fibrous histiocytoma-like features with spindle shaped cells growing in a storiform growth pattern devoid of the osteoclast-type giant cells. Other microscopic features include aggregates of foamy histiocytes, cystic (aneurysmal bone cyst-like) changes and reactive bone formation with osteoblastic rimming; rarely the bone formation is more lace-like without prominent osteoblastic rimming. Infrequently the mononuclear cells can demonstrate cytologic (degenerative) atypia with enlarged hyperchromatic nuclei. Tumor necrosis, especially in the setting of a pathologic fracture can be seen with necrosis of both the mononuclear and osteoclast type giant cells. Vascular invasion may be present and does not seem to be associated with more aggressive

behavior or metastatic deposits. The morphologic features of giant cell tumor of bone arising in younger individuals is similar⁶. Cartilage is rarely present. Soft tissue recurrence is commonly surrounded by a shell of reactive woven bone formation¹². Pulmonary metastases look like the primary giant cell tumor and, like soft tissue recurrence, may have a shell of reactive bone at the periphery.

The histologic response to denosumab is characterized by depletion of osteoclast-type giant cells and new bone formation with the morphologic features being related to the duration of treatment^{10,11}. Resected specimens after short course of treatment typically show a 'zoning' pattern with the central area composed of spindle shaped cells with osteoclast-type giant cells with fewer nuclei at the periphery and bone deposition. The central component demonstrated a storiform growth pattern with variable amount of lymphocytic infiltrate and foamy histiocytes; the cells can demonstrate cytologic atypia which should not be misinterpreted as sarcomatous transformation. At the periphery, there is bone deposition with osteoblastic rimming. Later during therapy the tumor shows decreased cellularity and is dominated by bone formation that is being deposited in long interconnecting strands. In the presence of a fracture in denosumab treated tumor there is a peculiar pattern of endochondral ossification simulating the morphologic features seen in osteopetrosis.

Immunohistochemical Findings.

The neoplastic mononuclear cells usually stain diffusely for p63¹³⁻¹⁵. This staining is not specific for giant cell tumor of bone as it can be seen in a variety of other giant cell rich tumors such as chondroblastoma, aneurysmal bone cyst, giant cell reparative granuloma and non-ossifying fibroma¹³⁻¹⁵. A subset of the mononuclear cells show nuclear staining for SATB2 (a marker for osteoblastic differentiation)¹⁶. Many of the mononuclear cells also stain for RANKL, supporting that they are of osteoblastic phenotype. The osteoclast-type giant cells stain for RANK. Recently immunohistochemical stain for the G34W mutated site of the histone H3.3 variant has been shown to be sensitive and specific to identify H3F3A mutation in giant cell tumor of bone, while the stain is negative in other tumor types in the differential diagnosis¹⁷. This antibody does not however detect other very rare mutations in giant cell tumor of bone (such as G34L, G34R or G34M). After denosumab therapy there is reduction in the staining for H3F3A; p63 staining highlights rare cells or can be altogether absent¹⁰.

Molecular and Other Special Techniques.

Ninety-six percent of giant cell tumor of bone demonstrate histone 3.3 mutation, exclusively in H3F3A, the vast majority being G34W. Very few other somatic changes have been identified, indicating that this represents an essential oncogenic driver. This has become of diagnostic utility in problematic cases, especially on small biopsy samples. The absence of mutation makes the diagnosis of a giant cell tumor of bone very unlikely.

Treatment.

Most tumors are treated with thorough curettage; intralesional curettage with polymethylmethacrylate seems to offer the best local control¹⁸. En bloc resection can be used for tumor that have destroyed the underlying bone or when resection causes minimal functional impairment such as for tumor arising in the proximal fibula and distal ulna. Radiation therapy is currently scarcely used because of effective drug therapy using denosumab. Denosumab is a monoclonal antibody antagonist against RANKL that can be used as an alternative therapy to a resection or a curettage, for treatment of tumors that are not easily

treated surgically (e.g., the sacrum) or in patients that might not tolerate an operation. Denosumab blocks the interaction between RANKL on the neoplastic mononuclear cells and RANK on the osteoclast precursors, inhibiting the formation of osteoclast-like giant cells and therefore bone resorption and destruction of the underlying bone.

Prognosis.

Approximately 25% of patients treated with curettage will develop local recurrence. Approximately 1-2% of giant cell tumor of bone will metastasize, usually to the lungs, and this is more common in patients with pathologic fracture and multiple recurrences treated with curettage. The metastatic disease is usually cured by resection; however rarely a patient may die from metastatic disease. Denosumab can also be used in the treatment of lung metastasis, causing mineralization, stabilization and even some reduction in the size of the metastatic deposits.

Differential Diagnosis.

A variety of benign and malignant giant cell rich tumors can mimic a giant cell tumor of bone and includes tumors such as non-ossifying fibroma (NOF), chondroblastoma, giant cell reparative granuloma, aneurysmal bone cyst and most importantly giant cell rich osteosarcoma. Giant cell tumor of bone can have areas resembling *NOF* with spindle cells growing in a storiform growth pattern. Radiographically, NOF has a very characteristic radiographic feature and is usually diagnosed in skeletally immature individuals. *Chondroblastoma* typically arises in skeletally immature individuals and although chondroblastoma and giant cell tumors of bone both involve the epiphysis, chondroblastoma is usually confined to the epiphysis, whereas giant cell tumor of bone usually also involves the adjacent metaphysis and even the diaphysis. The mononuclear cells in chondroblastoma have eccentric cleaved nuclei and eosinophilic cytoplasm and do not resemble the mononuclear cells in giant cell tumor of bone. Chicken wire calcifications are not seen in giant cell tumor of bone and chondroid areas are very rarely seen – both are commonly seen in chondroblastoma. Immunohistochemically, the mononuclear cells in chondroblastoma, but not in giant cell tumor of bone, stain for S100. Additionally, some of the mononuclear cells in giant cell tumor of bone stain for H3F3A whereas the mononuclear cells in chondroblastoma stain for H3F3B. *Giant cell reparative granuloma* arises in the jaw bones and small bones of the hand and feet. Unlike giant cell tumor of bone where the osteoclast-type giant cells are evenly distributed, in giant cell reparative granuloma the giant cells tend to cluster around areas of hemorrhage and the mononuclear cells are more spindle shaped; genetically many of the giant cell reparative granulomas of the small bones of the hands and feet are solid aneurysmal bone cysts. In primary *aneurysmal bone cyst* of bone, no underlying lesion is present; however, a giant cell tumor of bone may have extensive aneurysmal bone cyst-like changes obscuring the giant cell tumor especially on a small biopsy sample. In this setting USP6 mutational analysis and immunohistochemical stain for H3F3A may be helpful. In *giant cell-rich osteosarcoma*, the mononuclear cells demonstrate more cytologic atypia, abnormal mitotic figures, bone formation and an infiltrative growth pattern. Some giant cell-rich osteosarcomas may show immunohistochemical staining for H3F3A, like benign giant cell tumor of bone, suggesting that they may represent malignant giant cell tumor of bone instead of a separate tumor type¹⁹.

References

1. Jaffe HL, Lichtenstein L, Portis RB. Giant cell tumor of bone. Its Pathologic Appearance, Grading, Supposed Variants and Treatment. *Archives of Pathology*. 1940;30(5):993-1031.
2. Nielsen GP, Rosenberg AE, Deshpande V, Hornicek FJ, Kattapuram SV, Rosenthal DI. *Diagnostic Pathology. Bone*. Second ed. Philadelphia, PA: Elsevier; 2017.
3. *WHO Classification of Tumours of Soft Tissue and Bone*. 4th ed. Lyon: International Agency for Research on Cancer; 2013.
4. Czerniak B. *Dorfman and Czerniak's Bone Tumors*. Second Edition ed. Philadelphia, PA: Elsevier Saunders; 2016.
5. Unni KK, Inwards CY. *Dahlin's Bone Tumors*. 6 ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2010.
6. Al-Ibraheemi A, Inwards CY, Zreik RT, et al. Histologic Spectrum of Giant Cell Tumor (GCT) of Bone in Patients 18 Years of Age and Below: A Study of 63 Patients. *The American Journal of Surgical Pathology*. 2016;40(12):1702.
7. Sung HW, Kuo DP, Shu WP, Chai YB, Liu CC, Li SM. Giant-cell tumor of bone: analysis of two hundred and eight cases in Chinese patients. *J Bone Joint Surg Am*. 1982;64(5):755-761.
8. Hoch B, Inwards C, Sundaram M, Rosenberg AE. Multicentric giant cell tumor of bone. Clinicopathologic analysis of thirty cases. *The Journal of bone and joint surgery American volume*. 2006;88(9):1998-2008.
9. Campanacci M. Giant-cell tumor and chondrosarcomas: grading, treatment and results (studies of 209 and 131 cases). *Recent Results Cancer Res*. 1976(54):257-261.
10. Wojcik J, Rosenberg AE, Bredella MA, et al. Denosumab-treated Giant Cell Tumor of Bone Exhibits Morphologic Overlap With Malignant Giant Cell Tumor of Bone. *The American Journal of Surgical Pathology*. 2016;40(1):72.
11. Roitman P, Jauk F, Farfalli G, Albergo J, Aponte-Tinao L. Denosumab-treated giant cell tumor of bone. Its histologic spectrum and potential diagnostic pitfalls. *Human Pathology*. 2017;63:89-97.
12. Lee FY, Montgomery M, Hazan EJ, Keel SB, Mankin HJ, Kattapuram S. Recurrent giant-cell tumor presenting as a soft-tissue mass. A report of four cases. *The Journal of bone and joint surgery American volume*. 1999;81(5):703-707.
13. de la Roza G. p63 expression in giant cell-containing lesions of bone and soft tissue. *Archives of pathology & laboratory medicine*. 2011;135(6):776-779.
14. Dickson BC, Li S-Q, Wunder JS, et al. Giant cell tumor of bone express p63. *Modern Pathology*. 2008;21(4):369-375.
15. Lee C-H, Espinosa I, Jensen KC, et al. Gene expression profiling identifies p63 as a diagnostic marker for giant cell tumor of the bone. *Modern Pathology*. 2008;21(5):531-539.
16. Conner JR, Hornick JL. SATB2 is a novel marker of osteoblastic differentiation in bone and soft tissue tumours. *Histopathology*. 2013;63(1):36-49.

17. Lüke J, Baer A, Schreiber J, et al. H3F3A mutation in giant cell tumour of the bone is detected by immunohistochemistry using a monoclonal antibody against the G34W mutated site of the histone H3.3 variant. *Histopathology*. 2017;71(1):125-133.
18. Klenke FM, Wenger DE, Inwards CY, Rose PS, Sim FH. Giant Cell Tumor of Bone: Risk Factors for Recurrence. *Clinical Orthopaedics and Related Research*®. 2011;469(2):591-599.
19. Amary F, Berisha F, Ye H, et al. H3F3A (Histone 3.3) G34W Immunohistochemistry: A Reliable Marker Defining Benign and Malignant Giant Cell Tumor of Bone. *The American journal of surgical pathology*. 2017;41(8):1059-1068.