Giant Cell–Containing Tumors of Bone

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KEYWORDS

• Giant cell tumors • Bone • Osteoclast

Key points

- Histologic appearances of different giant cell–containing lesions, especially in biopsy samples, can be significantly overlapping. For correct diagnosis, it is essential to take into consideration the age of the patient, location of the lesion, radiologic findings, comorbidities, and laboratory results.
- The distribution of the giant cells, appearance of mononuclear cells, presence or absence of mitotic activity, presence or absence of atypical mitoses, and the quality of the stroma are important cornerstones to the correct diagnosis.
- Immunohistochemical analysis of giant cell tumors (GCTs) led to the discovery of the receptor activator for nuclear factor κB (RANK) and to the development of targeted therapy for GCT of bone by denosumab.
- Molecular profiling of histone H3.3 variant resulted in the diagnostically useful K36M antibody for chondroblastoma identification.

ABSTRACT

Giant cell–containing tumors of bone are characterized morphologically by the presence of numerous osteoclastic giant cells. Correlation of clinical, radiologic, and laboratory findings is required for accurate histopathologic diagnosis and treatment of a giant cell–containing tumor of bone. In differential diagnosis, it is particularly important to note the age of the patient and the skeletal location of the lesion. This review considers the range of neoplastic and non-neoplastic lesions, which histologically contain numerous osteoclastic giant cells, and focuses on several lesions that frequently enter into the differential diagnosis.

OVERVIEW

Giant cell–containing tumors of bone (GCTs) represent a large category of tumors and tumor-like lesions, which are characterized morphologically by the presence of numerous osteoclasts or osteoclast-like giant cells. Osteoclasts are formed by the fusion of mononuclear phagocyte (macrophage) precursors, which express receptor activator for nuclear activator κB (RANK).[1] In the presence of macrophage-colony stimulating factor, these cells interact with osteoblasts that express RANK ligand (RANKL) and differentiate into multinucleated osteoclasts. There is a decoy receptor for RANKL, termed *osteoprotegerin*, which inhibits osteoclast formation/activity. Numerous cytokines and growth factors, including tumor necrosis factor α and interleukin 6, promote RANKL-induced osteoclast formation/activity. Mononuclear stromal cells in giant cell tumor of bone (GCTB) and other GCTs express RANKL.[2–4]

Several discrete neoplastic and non-neoplastic lesions of bone enter into the differential diagnosis of a GCT (**Box 1**). For this reason, correlation of histology with clinical, radiologic, and laboratory findings is essential for diagnosis. It is particularly

Disclosure Statement: There are no commercial or financial conflicts of interest. No funding has been received for this work.

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Surgical Pathology ■ (2017) ■–■

http://dx.doi.org/10.1016/j.path.2017.04.004

Box 1
Bone lesions containing numerous osteoclasts/osteoclast-like giant cells

- GCTB
- Chondroblastoma
- CMF
- ABC
- LCH
- NOF
- Giant cell reparative granuloma (jaw/small bones)
- FD
- Giant cell–rich osteosarcoma
- Telangiectatic osteosarcoma
- Simple bone cyst (with fracture)
- Other bone tumors (eg, osteoblastoma) associated with excessive bone remodeling activity
- Paget disease
- Fracture
- Hyperparathyroidism (brown tumor)

important to note patient age because certain GCTs occur more commonly in skeletally mature or immature patients (**Table 1**). GCTs present with pain and/or swelling but a few can present with a pathologic fracture. Laboratory investigations, such as serum calcium and phosphate, are often useful to exclude a metabolic disorder, such as hyperparathyroidism.

The precise location of a GCT within bone provides important diagnostic information (see **Table 1**). GCTB and chondroblastoma typically involve the epiphysis of a long bone and it is always important to exclude these lesions when dealing with an epiphyseal GCT. Other radiologic features useful to note include whether the growth plate is open or closed, whether the bone containing the lesion is normal or abnormal, and whether the zone of transition, that is, the interface between the lesion and the surrounding bone, is well or poorly defined. A sclerotic rim is present around a very slow growing tumor whereas a nonsclerotic margin is usually found around a more rapidly growing lytic lesion. It may be possible to radiologically identify specific matrix components, such as bone and cartilage, or calcification within the lesion. Rapidly growing malignant lesions are evidenced by destruction of the host bone by

Table 1
Age groups and involved sites of giant cell tumors

	Most Commonly Involved Age Group	Most Commonly Involved Sites
GCTB	Third and fourth decades	Epiphysis of femur, tibia, humerus
Chondroblastoma	Skeletally immature patients	Epiphysis of femur, tibia, and humerus
ABC	Most common but not exclusive in skeletally immature patients	Metaphysis of long bones Lumbar and cervical vertebrae
Giant cell lesion of the small bones	Children, adolescents, and young adults	Hands and feet
Brown tumor of hyperparathyroidism	Skeletally mature patients	Hands, facial bones, pelvis, ribs, femur
NOF	Children, adolescents, young adults	Metaphysis of femur, tibia, fibula, humerus
LCH	First decade of life	Skull, jaws, ribs, vertebrae, proximal long bones
CMF	Adolescent, young adults	Metaphysis of long bones, proximal tibia, bones of the feet
FD	First 3 decades	Skull, facial bones, jaw, rib, pelvis, metaphysis of femur and tibia
Telangiectatic osteosarcoma	Second decade	Distal femoral metaphysis, proximal tibia, proximal humerus