Journal of Research and Practice on the Musculoskeletal System
JRPMS

Mini Review

Malignant giant cell tumor of bone

Emmanouil Neonakis[1], Georgia Antoniou[1], Ioannis K. Triantafyllopoulos[2]

[1]"Agia Sofia" General Children's Hospital, Division of Orthopedic Surgery, Athens, Greece; [2]Laboratory for Research of the Musculoskeletal System, National and Kapodistrian University of Athens, Greece

Abstract

Giant cell tumors of bone are locally destructive benign entities that occur predominantly in long bones of post-pubertal adolescents and young adults. The majority are treated by aggressive curettage or resection. Occasionally, Giant cell tumors of bone may undergo malignant transformation to undifferentiated sarcomas. We report a mini review of malignant GCT of the long bones in order to raise awareness of this entity that may mimic the benign form but is more aggressive with poorer prognosis.

Keywords: Giant cell tumor, Long bones, Malignant transformation

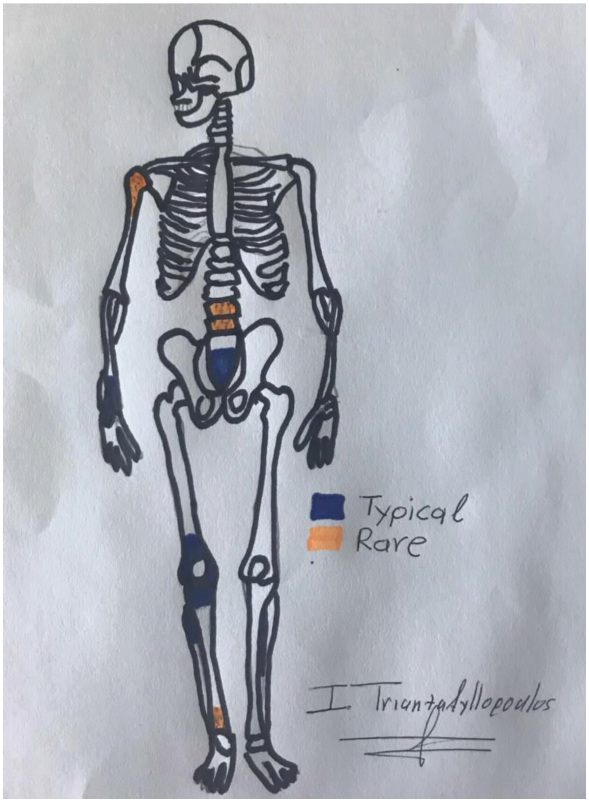


Figure 1. Typical and less typical locations of Giant cell tumors of long bones.

Giant cell tumors (GCTs) are primary locally aggressive bone tumors that represent 5% of all bone neoplasms[1]. They have a female predominance and they are most common in patients aged 20 to 40 years. In Oriental and Asian populations incidence may reach 20% of bone neoplasms while it is more uncommon in Caucasians[2]. Pain is the most common presenting symptom while pathologic fractures may occur in 11-37% of the cases[3]. Distal femur, proximal tibia and distal radius are the most common sites involved with 50% of the cases diagnosed around the knee area[4] (Figure 1). These neoplasms are characterized by osteoclast-like giant multinucleate cells (Figure 2). Thus, radiographically they appear as pure osteolytic eccentric lesions of the epiphysis extending to the articular surface or the diaphysis (Figure 3)[5]. GCTs are usually highly destructive solitary lesions commonly extending to the surrounding soft tissue, however 1% to 2% may simultaneously or sequentially be multicentric[6].

Although classified as primary benign bone tumors, in 1-3% of GCTs spontaneous transformation to a high-grade

The authors have no conflict of interest.

Corresponding author: *Emmanouil Neonakis, Thessalonikis 97 Piraeus, Greece*

E-mail: *neonakisemmanouil@gmail.com*

Edited by: *Konstantinos Stathopoulos*

Accepted *13 March 2019*

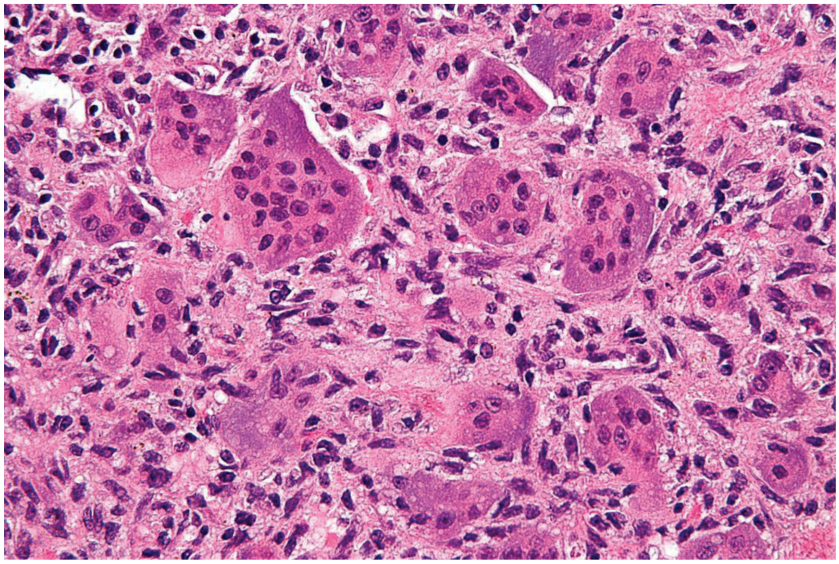
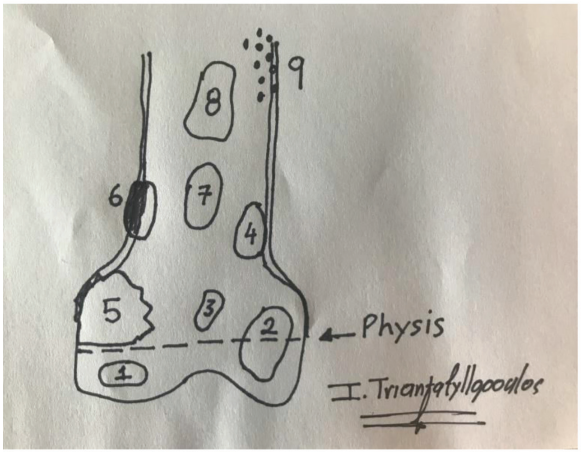


Figure 2. High magnification micrograph with H&E staining, of giant cells in a giant-cell bone tumor.



1. Chondroblastoma
2. **Giant cell tumor**
3. Enchondroma
4. Non-ossifying fibroma
5. Osteosarcoma
6. Chondromyxoid fibroma
7. Solitary bone cyst
8. Fibrous dysplasia
9. Round cell lesions

Figure 3. Topographic differential diagnosis of giant-cell tumor with other bone tumors.

malignancy may occur[4]. This malignant transformation may be found in both primary and secondary GCTs, but it is more common in secondary GCTs whom recur at the same site years after surgical excision or radiotherapy[7]. The incidence of malignant GCTs has been estimated in the United States at 2.4 per 10000000 persons per year (mainly adults aged 20 to 44 years of age) and malignant transformation unfortunately leads to a poor prognosis, similar to the one of high-grade sarcomas[8].

The differential diagnosis of malignant GCTs is extremely difficult and important due to their aggressive character and poor prognosis compared to the benign forms[1]. The difficulty in the interpretation of these lesions begins with terminology. The term malignant GCTs has been controversial due to its usage to describe several entities such as giant cell-rich osteosarcomas and malignant fibrous histiocytomas with multinucleated cells which are not GCTs[7]. As a result, throughout the years, various studies and scientific teams

have attempted to establish criteria to classify malignant GCTs. Turning his focus on the pathophysiology of the lesion rather than its clinical manifestation, Jaffe was the first to identify a unique morphology in which the stromal mononucleated cells showed noticeable atypia[9]. Nachimento later proposed that for the definitive diagnosis of malignant GCTs there should be significant areas of high grade non-osteogenic sarcoma characteristics within the stromal component of the lesion[10]. Atypia, as well as coagulative necrosis, vascular emboli and metastasis which are criteria for malignancy are not applicable in malignant GCTs since even the benign forms may exhibit theme[1,10]. Histologically, cells with hyperchromatic nuclei with variably prominent nucleoli, atypical mitoses and malignant spindle cells may also be found infiltrating the normal bone trabecula[11,12]. A careful dissection of the pathologic tissue taken to biopsy along with a simple hematoxylin and eosin dye may reveal the malignant areas of transformed GCTs[12]. Furthermore, immunohistochemistry revealing over-expression of P53, P63 and Ki67 has been associated with malignant transformation[11,13,14].

When investigating malignant GCTs, it is important to underline the separation between primary and secondary malignant GCTs. Primary malignant GCTs are extremely rare, characterized by a spontaneous malignant transformation of conventional GCTs to lesions with sarcomatous features after the initial diagnosis[12,15]. The most recent term for this entity is "malignancy in giant cell tumor"[16]. On the other hand, secondary malignant GCTs are lesions characterized by malignant transformation in patients previously treated with surgical excision or radiotherapy GCTs[7,15,17]. The exact pathophysiologic mechanism of this transformation remains unknown, but studies have shown that secondary malignant GCTs tend to be more aggressive than the primary ones[6,9]. Additionally, patients with secondary malignant GCTs post radiotherapy tend to have worst prognosis and thus are monitored closely[16,18,19]. For secondary malignant GCTs malignant transformation may take 4 to 40 years[5,6,18].

Radiology and clinical evaluation of benign and malignant GCTs may not differentially diagnose one form from the other since they both exhibit signs of osteolysis, cortical erosion and soft tissue involvement[7,20]. This separation is simplistic though, since benign GCTs demonstrate a 5-year survival of 90% and are treatable, unlike the malignant forms[21-23]. Even benign metastatic GCTs have better survival rates[24].

On the other hand, distinction from "giant cell-rich" or "osteoclasts-rich" osteosarcomas which are associated with osteoclast-like giant multinucleated cells and hence have similar pathophysiological characteristics, is aided by radiological characteristics such as the site of the tumor, its diaphyseal or meta-diaphyseal location[25]. Other sarcomas containing giant cells that should be included to the differential diagnosis are osteosarcoma, chondrosarcoma, fibrosarcoma and undifferentiated high grade pleomorphism sarcoma[7].

The treatment of choice is surgery depending on the extension of the lesion but since this is a rare entity no established treatment algorithm has been designed[26]. En block excision is the optimal treatment option which is designed based on modern imaging techniques such as Magnetic Resonance Imaging (MRI) but may be extensive and disabling for the patient[10,27]. Yin et al. in their series of 14 patients reported statistically significant lower local recurrence rates of malignant GCTs of the spine with total en bloc spondylectomy compared to subtotal or piecemeal total resections[28]. In the series of Kapoor SK et al., patients that developed malignant GCT and treated with en bloc excision, died within 5 months post diagnosis[29]. Investigators have used chemotherapy alone in non-operable cases while Denosumab which is a monoclonal antibody to RANKL has been additionally used for palliative treatment. Thomas DJ et al. reported excellent results of denosumab administration in reducing pain in nearly 85% of patients and minimizing radiographic progression of the lesion in almost 90% of the cases[30]. Additionally, in phase II study trials, treatment with Denosumab has been shown to inhibit disease progression and reduce requirement of surgery while inducing tumor necrosis of GCT[31]. However, these were benign GTC cases in which surgical excision due to location and extend was not possible[31,32]. Furthermore, in all these data, researchers question the duration of Denosumab treatment needed and the recurrence rates of GCT after the mononuclear antibody is stopped[32]. The recurring GCT after Denosumab treatment may be malignant but the exact incidence is unknown thus the eligibility of Denosumab in malignant GCTs remains a question to be answered in future studies[33].

Conclusion

GCT of long bones is classified as benign neoplasm. Malignant transformation has a difficult clinical and radiographic diagnosis and may only be diagnoses histologically. Malignant components are usually sparse within the benign components and are likely to be missed on biopsy. Thus, careful biopsy supplementation by orthopaedic surgeons and a throughout examination by pathologists is critical for diagnosis. Proper treatment by wide excision should be performed when possible to offer these patients the best possible care. Hopefully, further investigation of agents such as denosumab with excellent results for benign forms of GCTs will add to our treatment options in the future. Currently, awareness, high rates of suspicion and early detection are the key ingredients in the treatment of malignant GCTs.

References

1. Unni KK, Inwards CY, Bridge JA, Kindblom LG, Wold LE. Tumors of the bones and joints. In: Atlas of Tumor Pathology. Series 4. Washington: Armed Forces Institute of Pathology; 2005.
2. Settakorn J, Lekawanvijit S, Arpornchayanon O, Rangdaeng S, Vanitanakom P, Kongkarnka S, Cheepsattayakorn R, Ya-In C, Thorner PS. Spectrum of bone tumors in Chiang Mai University Hospital,

Thailand according to WHO classification 2002: A study of 1,001 cases. J Med Assoc Thai 2006; 89(6):780-7.
3. Campanacci M, Giuti A, Olmi R. Metaphyseal and diaphyseal localization of giant cell tumors. Chir Organi Mov 1975;62(1):29-34
4. Unni, K. Krishnan, and Carrie Y. Inwards. Malignancy in Giant Cell Tumor of Bone. Dahlin's Bone Tumors: General Aspects and Data on 10,165 Cases. Philadelphia: Wollters Kluwer Health/Lippincott Williams & Wilkins, 2010.
5. Hutter RV, Worcester JN Jr, Francis KC, Foote FW Jr, Stewart FW. Benign and malignant giant cell tumors of bone. A clinicopathological analysis of the natural history of the disease. Cancer 1962;15:653-90.
6. Thomas David M, Keith M. Skubitz. Giant Cell Tumour of Bone. Current Opinion in Oncology 2009; 21(4): 338-44.
7. Bertoni F, Bacchini P, Staals EL. Malignancy in giant cell tumor of bone. Cancer 2003;97(10):2520-9.
8. Beebe-Dimmer JL, Cetin K, Fryzek JP, Schuetze SM, Schwartz K. The epidemiology of malignant giant cell tumors of bone: an analysis of data from the Surveillance, Epidemiology and End Results Program (1975-2004). Rare Tumors 2009; 1(2):e52.
9. Jaffe HL. Giant-cell tumour (osteoclastoma) of bone: its pathologic delimitation and the inherent clinical implications. Ann R Coll Surg Engl 1953;13(6):343-55.
10. Nascimento AG, Huvos AG, Marcove RC. Primary malignant giant cell tumor of bone: a study of eight cases and review of the literature. Cancer 1979;44(4):1393-402.
11. Gong Lihua, Weifeng Liu, Xiaoqi Sun, Constantin Sajdik, Xinxia Tian, Xiaoyuan Huang. Histopathological and Clinical Characteristics of Malignant Giant Cell Tumor of Bone. Virchow Archiv 2012;460(3): 327-34.
12. Megan Greene, Carrie Y. Inwards Malignant Transformation of Giant Cell Tumor: A case study. Mayo Clinic Rochester MN.
13. Alberghini M, Kliskey K, Krenacs T, Picci P, Kindblom L, Forsyth R, Atnanasou NA. Morphological and immunophenotypic features of primary and metastatic giant cell tumour of bone. Virchows Arch 2010;456:97-103.
14. Lee CH, Espinosa I, Jensen KC, Subramanian S, Zhu SX, Varma S, Montgomery KD, Nielsen TO, van de Rijn M, West RB. Gene expression profiling identifies p63 as a diagnostic marker for giant cell tumor of the bone. Mod Pathol 2008;21:531-9.
15. Grote M. Braum, T Kalinski, N Pomjanski, W Back, U Bleyl, A Bocking, A Roessner. Spontaneous malignant transformation of conventional giant cell tumor Skeletal Radiol 2004; 33(3):169-75.
16. Dahlin DC, Cupps RE, Johnson EW Jr. Giant-cell tumor: A study of 195 cases. Cancer 1970;25:1061-70.
17. Unni KK. How to diagnose malignant giant cell tumor. Pathology Case Reviews 2001;6(1):33-7.
18. Anract P, de PG, Cottias P, Pouillart P, Forest M, Tomeno B. Malignant giant-cell tumours of bone. Clinicopathological types and prognosis: a review of 29 cases. Int Orthop 1998;22:19–26.
19. Unni K.K. Dahlin's bone tumor: general aspects and data on 11,087 cases. 5th edition. Philadelphia: Lippincott-Raven Publishers; 1996.
20. Scully SP, Mott MP, Temple HT, O'Keefe RJ, O'Donnell RJ, Mankin HJ. Late recurrence of giant-cell tumor of bone. A report of four cases. J Bone Joint Surg Am 1994;76(8):1231–3.
21. Mendenhall WM, Zlotecki RA, Scarborough MT, Gibbs CP, Mendenhall NP. Giant cell tumor of bone. Am J Clin Oncol 2006;29(1):96-9.
22. Ward WG Sr, Li G 3rd. Customized treatment algorithm for giant cell tumor of bone: report of a series. Clin Orthop Relat Res 2002;(397):259-70.
23. Keith M. Giant cell tumor of bone: current treatment Options " current treatment options in oncology (2014): n. Pag.Springer Link Web 27 June 2014
24. Viswanathan, Seethalakshmi and N.A. Jambhekar. Metastatic Giant Cell Tumor of Bone: Are There Associated Factors and Best Treatment Modalities?. Clinical Orthopaedics and Related Research 2010; 468(3):827-33.
25. Bathurst N, Sanerkin N, Watt I. Osteoclast-rich osteosarcoma. Br J Radiol 1986;59(703):667-73.
26. Skubitz KM. Giant Cell Tumor of Bone: Current Treatment Options. Curr Treat Options Oncol 2014;15(3):507-18.
27. D. Cheong, G. Douglas Letson. Giant Cell Tumor of Bone. Orthopaedic Knowledge: Myoskeletal Tumors 3 Chapter 13 p.133-142.
28. Yin H, Cheng M, Li B, Li B, Wang P, Meng T, Wang J, Zhou W, Yan W, Xiao J. Treatment and outcome of malignant giant cell tumor in the spine. J Neurooncol 2015;124(2):275-81.
29. Kapoor SK, Jain V, Agrawal M, Singh S, Mandal AK. Primary malignant giant cell tumor of bone: a study of three rare cases. J Surg Orthop Adv 2007 Summer; 16(2):89-92
30. Thomas DJ, Chawla S, Skubitz K, Staddon A, Henshaw R, Blay J, Smith, et al. Denosumab for the treatment of giant cell tumor of bone: Final results from a proof-of-concept, phase II study. Clin J Oncol 2009;27[538S]
31. SF Xu, B Adams, XC Yu, M Xu. Denosumab and giant cell tumour of bone -a review and future management considerations Curr Oncol 2013;20(5):e442-7.
32. Gaston CL, Robert JG, Michael Parry, et al. Current status and unanswered questions on the use of Denosumab in giant cell tumor of bone. Clin Sarcoma Res 2016; 6:15
33. Aponte-Tinao LA, Piuzzi NS, Roitman P, Farfalli GL. A high-grade sarcoma arising in a patient with recurrent benign giant cell tumor of the proximal tibia while receiving treatment with Denosumab. Clin Orthop Relat Res 2015;473(9):3050–5.