International Journal of Research in Orthopaedics
Channappa TS et al. Int J Res Orthop. 2023 May;9(3):611-615
http://www.ijoro.org

DOI: https://dx.doi.org/10.18203/issn.2455-4510.IntJResOrthop20231193

Case Report

Malignant transformation of a recurrent giant cell tumor of bone with lung metastasis: a case report

T. S. Channappa*, H. B. Shivakumar, Manju Jayaram, Yatish R., Surya Teja

Department of Orthopaedics, KIMS, Bangalore, Karnataka, India

Received: 04 March 2023
Revised: 05 April 2023
Accepted: 06 April 2023

***Correspondence:**
Dr. T. S. Channappa,
E-mail: drchannappagowda@gmail.com

ABSTRACT

Giant cell tumors (GCT) are benign tumors with potential for aggressive behaviour and capacity to metastasize. It is a locally destructive tumor that occurs predominantly in long bones of adolescents and young adults in the epiphysis. Although rarely lethal, benign bone tumors may be associated with a substantial disturbance of the local bony architecture that can be particularly troublesome in peri-articular locations. It is characterized by a proliferation of mononuclear stromal cells and the presence of many multi-nucleated giant cells with homogenous distribution. There are varying surgical techniques ranging from intra-lesional curettage to wide resection. As most giant cell tumors are benign and are located near a joint in young adults, several authors favour an intralesional approach that preserves anatomy of bone. Although GCT is classified as a benign lesion, few patients develop progressive lung metastases with poor outcomes. Malignant transformation without radiotherapy exposure, is an uncommon event, occurring in less than 1% of giant cell tumors of bone. Here we reported a case of recurrent GCT of tibia that at the time of final recurrence was found to have undergone malignant transformation over a period of 6 years following several limb salvaging procedures. Concurrent metastases were found in the lung, but these were non-transformed GCT following which the patient has undergone above knee amputation.

Keywords: GCT, Metastasis, Curretage and bone grafting, Bone cement

INTRODUCTION

GCTs are generally of benign nature. Most of these involve proximal part of long bone, that is, proximal tibia proximal fibula, occurance of this type of tumor is peak in 3rd decade, 30 to 40 years of age. Very few of these tumors are local invasive in nature, detail investigations like FNAC and histopathology are required when palpable swelling is observed in such cases.

There is no widely held consensus regarding the selection of an ideal treatment method. There are advocates of varying surgical techniques ranging from intra-lesional curettage to wide resection. Although GCT is classified as a benign lesion, few patients develop progressive lung metastases with poor outcomes.

Histologically, GCT of bone classically shows many large multinucleated giant cells interspersed with haphazardly arranged mononuclear stromal cells, with both elements having similar nuclear features. Malignant transformation in a histologically typical GCT of bone, without radiotherapy exposure, is an uncommon event, occurring in less than 1% of giant cell tumors of bone.

On occasion, GCTs of bone undergo malignant transformation to undifferentiated sarcomas. The rate of local recurrence varies among centers and is influenced by the completeness of surgical treatment, with high speed

burring, adjuvants, and bone cement adding to the effectiveness of curettage treatment.[1] Unresectable tumors such as large sacral masses can be treated with radiation.[2] New therapies targeting the receptor activator of NF-B (RANK) signaling pathway, such as with the anti-RANK ligand antibody denosumomab are in early stages of investigation.[3]

Here, we reported a case of GCT of bone that at the time of recurrence was found to have undergone malignant transformation. Concurrent metastases were found in the lung, but these were non-transformed GCT.

CASE REPORT

In August 2014, a 38-year-old lady presented to our hospital with complaints of pain on the medial side of the left knee, especially at night. Radiographs showed an expansile, eccentric, osteolytic lesion involving the medial tibial condyle, with a wide zone of transition giving a soap bubble appearance, with suspicious cortical. There was no evidence of soft tissue swelling/periosteum reaction. MRI knee showed evidence of an expansive, osteolytic lesion with a narrow zone of transition in the subarticular epiphyseal region of tibia.

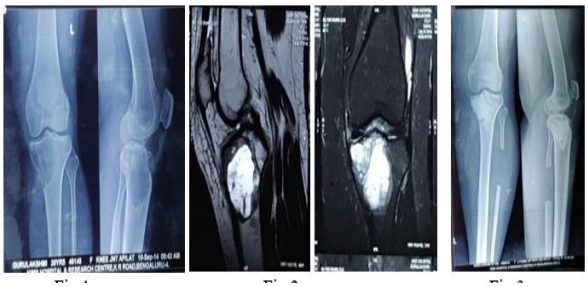

Figure 1: 1 year post-op.

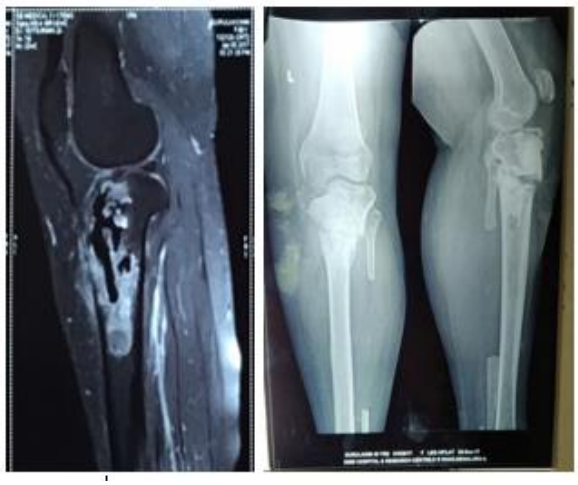

Figure 2: 10 months post-op.

T2 imaging showed hyperintense cystic lesions, giving the soap bubble appearance with significant enhancement. Subtle peri osseous soft tissue enhancement was noted.

She underwent intralesional curretage with fibular and iliac bone graft and cement.

HPE showed features suggestive of a GCT.

Patient was regularly followed up.

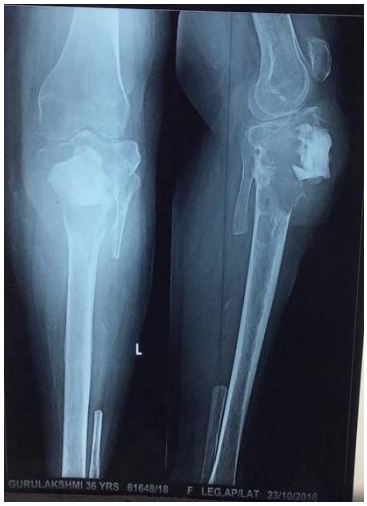

Figure 3: 3.5 years postop.

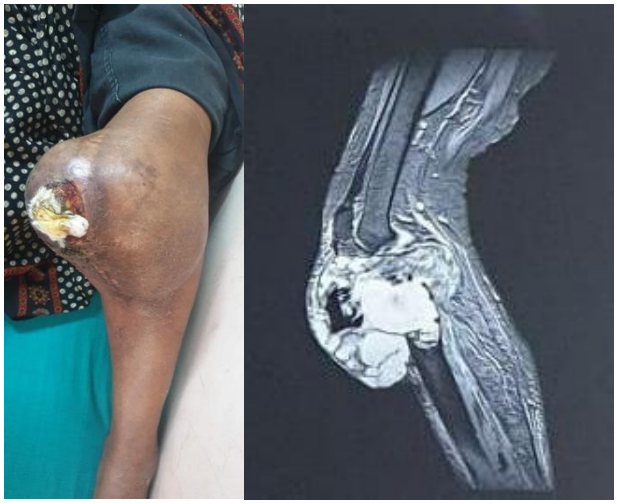

Figure 4: Clinical and MRI images 2019.

Patient again presented in October 2018 with severe pain and swelling at the site of previous excision. MRI revealed expansive osteolytic lesion with narrow zone of transition in subarticular meta-epiphyseal region of tibia. There were extensions to articulate surface with breach and erosions with infiltrations of articulation cartilage, malignant transformation.

Enhancing synovial thickening was noted. Hypo intense part was bone cement. Endosteal scalloping and thinning of cortex were noted.

Patient was advised limb salvage procedure but due to financial constraints patient refused further treatment.

A year later in October 2019, patient presented with severe pain and disability with radiographs showing an osteolytic lesion noted involving proximal shaft of tibia with a wide zone of transition, cortical breach, bone cement and soft tissue swelling. MRI revealed large lobulated expansive multi septated lytic lesion involving meta epiphyseal subarticular part of upper end of tibia. Measured 15×11 cm. Patient showed heterogenous intensity and septal enhancement, with prominent cavitation, soap bubble appearance with fluid intensity. Hypointense areas s/o bone cement. PET CT revealed multiple well defined and irregular bilateral lung nodules s/o metastasis.

On 24 October 2019, patient underwent above knee amputation.

Gross specimen showed many cystic and hemorrhagic areas, rimmed by thin cortical bone and adjacent soft tissue.

HPE was malignant GCT.

Pathological findings

Histological examination in 2014 revealed tissue fragments composed of blood filled cystic spaces, rimmed by numerous multinucleated giant cells and fibroblasts. In other areas, the cells were more spindle-shaped and were arranged in interwoven bundles and MNG cells were not distributed throughout.

In 2019, the tissue sent for histopathological evaluation showed that multi nucleated giant cells (MNG) were not uniformly spread throughout the stroma. MNG's contain 10-20 nuclei and nuclei of MNG's resemble nuclei of stromal cells. A few blood filled cystic spaces, rimmed by multinucleated giant cells and fibroblasts were also found in these areas- ABC like areas. A few areas of fibrosis and bone reaction were seen. The above findings gave a histological diagnosis of GCT.

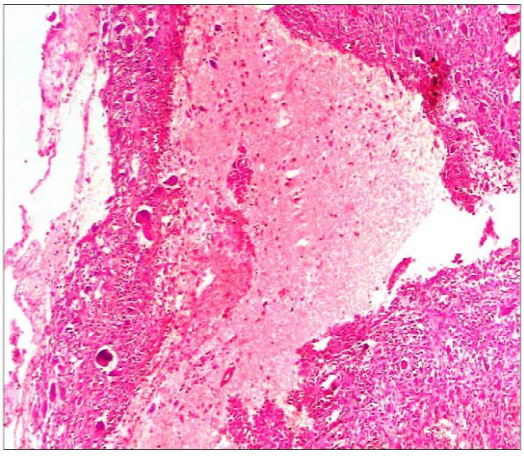

Figure 5: Blood filled cystic spaces, rimmed by multinucleated giant cells and fibroblasts.

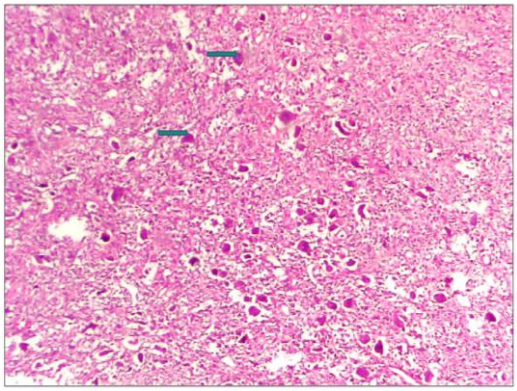

Figure 6: Multinucleated giant cells are uniformly spread throughout the stroma.

DISCUSSION

GCTs of bone are neoplasms of stromal cells that recruit a mononuclear population of hematopoietic origin.[4] These monocytes and/or multinucleated giant cells may in turn produce factors that support growth of the stromal cells, but this has not been explored. The oncocyte derived component was highlighted in immunohistochemical stains for the lysosomal marker CD68 and for monocyte lineage specific markers. The lineage of the stromal cells is still poorly characterized, but a subset variably expresses alkaline phosphatase, similar to osteoblasts.[5] Factors such as monocyte colony stimulating factor (m-CSF) and RANK ligand, which are important for osteoclastogenesis and for fusion of monocytes to form multinucleated giant cells, are expressed in giant cell tumors of bone.[6] Presumably the stromal cells are the source of m-CSF, akin to the situation in localized and diffuse giant cell tumors of tendon sheath/synovium where m-CSF is overexpressed by the neoplastic cells, sometimes secondary to a recurrent translocation.[7,8] Accordingly, cultured giant cell tumor stromal cells are chemoattractant to peripheral blood monocytes.[9]

In karyotypic analysis of giant cell tumors of bone, end-to-end fusions of various chromosomes, termed telomeric associations, are seen in most tumors in a subset of cells, and these have been localized by FISH studies to the CD68 negative spindled stromal component.[10] At lower frequency than telomeric associations, clonal chromosome gains, deletions and translocations can also be found in GCT of bone.[11] Translocations occur more frequently in tumors that have more telomeric associations, and they probably result from ensuing problems in separation of dicentric chromosomes during telophase.[11] However, cells with chromosomal abnormalities do not have enough of a growth advantage to dominate the tumor population, and analyses of many metaphases is required to recognize that there are clonal subpopulations in the tumor.[11] In Goronova's study there was no association between karyotype and prognosis.[11] Also, no dominant recurrent cytogenetic abnormality was seen that might give clues to pathogenesis. Thus, this peculiar low level chromosome

instability reflects an underlying defect in chromosome maintenance, though probably not due to a generalized defect in telomerase activity.[12] The minor genomic instability seen *in vitro* was reflected by a low but definite probability of transformation clinically, as seen here. However, because of the current lack of a defined molecular or cytogenetic marker of GCT of bone, formal proof that the rare cases of malignant transformation were due to evolution of the spindle cells of GCT of bone was lacking. An alternative hypothesis would be that that GCT of bone predisposes to malignancy in an unrelated cell-akin to secondary malignancy in the setting of osteonecrosis or Paget's disease of bone. Notably, cases were considered secondary malignant giant cell tumors even if, on recurrence, only the malignant component was seen.

This case illustrated a sarcoma arising at the site of a locally recurrent GCT of bone, with concurrent non-sarcomatous metastases. Local recurrence of GCT of bone was common, occurring 10-20% of the time, and depended on the aggressiveness of the initial surgery.[13-16] Metastasis with benign morphology, most commonly to the lung, was reported in an average of 3% of cases, and more than half occurred in patients who also had local recurrence.

Diagnosis of transformation relied on overt malignant cytological features, as necrosis and scattered mitoses can be seen in the usual benign GCT of bone. Immunohistochemical studies were not required for the diagnosis of transformation. Usually there was no evident lineage of maturation, but cases of osteosarcoma had been reported.[17-21,23] The incidence of malignancy in GCT varied considerably among studies, with an overall rate of approximately 5% considering the largest series together. About half were associated with prior irradiation, but transformation was found in the initial resection in about one third of cases. Secondary transformation had a latency of up to 28 years in a case that without radiotherapy.[17] Given the wide range of reported incidence of malignancy in GCT of bone among studies, it was probable that this entity had been over diagnosed in the reported series. Of note, in the publications with the highest rates of malignancy, there was no pathological slide review. In Bertoni's study, pathological review was performed and as a result, the initial diagnosis was revised to something other than malignant transformation of giant cell tumor in 12 of 26 cases initially considered for which slides were available.[17] Anract's study which did not include pathological review, included 5 cases with well differentiated fibrosarcoma, which was much different from the more widely recognized high grade transformation.[24] Likewise, in Domovitov's report 57% of the cases had the curious diagnosis of focally malignant histology. Accordingly, the outcomes in their study were optimistic, with 80% of patients predicted to be recurrence free at 5 years based on their data, compared to the 10-50% overall survival estimated in most other series. Thus, excluding radiation-induced transformation cases, and considering only series with pathological review, the incidence of malignant transformation of GCT of bone is only about 1%, which was the rate cited in the WHO publication.[22]

CONCLUSION

We report here the case of a giant cell tumor of the proximal tibia of a 38-year-old lady treated with aggressive curettage that recurred 5 years later with malignant transformation and benign metastases to the lung. Recurrence, malignant transformation, and metastasis with benign morphology all occur in GCT of bone. All these three occurring in a single patient has only been reported once till date. The influence of local recurrence on malignant transformation and pulmonary metastases is largely unknown. Malignant transformation has been reported most frequently with radiation even in non recurrent tumors. Similarly, benign pulmonary metastases have been reported to occur in recurrent and nonrecurrent tumors. The current report adds little to the discussion of the fate of locally recurrent giant cell tumor of bone. The molecular pathways leading to giant cell tumors of bone are still largely uncharacterized.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Balke M, Schremper L, Gebert C, Ahrens H, Streitbuerger A, Koehler G, et al. Giant cell tumor of bone: treatment and outcome of 214 cases. J Cancer Res Clin Oncol. 2008;134(9):969-78.
2. Caudell JJ, Ballo MT, Zagars GK, Lewis VO, Weber KL, Lin PP, et al. Radiotherapy in the management of giant cell tumor of bone. Int J Radiat Oncol Biol Phys. 2003;57(1):158-65.
3. Thomas DM, Skubitz KM. Giant cell tumour of bone. Curr Opin Oncol. 2009;21(4):338-44.
4. Werner M. Giant cell tumour of bone: morphological, biological and histogenetical aspects. Int Orthop. 2006;30(6):484-9.
5. Morgan T, Atkins GJ, Trivett MK, Johnson SA, Kansara M, Schlicht SL, et al. Molecular profiling of giant cell tumor of bone and the osteoclastic localization of ligand for receptor activator of nuclear factor kappaB. Am J Pathol. 2005;167(1):117-28.
6. Atkins GJ, Haynes DR, Graves SE, Evdokiou A, Hay S, Bouralexis S, et al. Expression of osteoclast differentiation signals by stromal elements of giant cell tumors. J Bone Miner Res. 2000;15(4):640-9.
7. Cupp JS, Miller MA, Montgomery KD, Nielsen TO, O'Connell JX, Huntsman D, et al. Translocation and expression of CSF1 in pigmented villonodular syn vitis, tenosynovial giant cell tumor, rheumatoid arthritis and other reactive synovitides. Am J Surg Pathol. 2007;31(6):970-6.
8. West RB, Rubin BP, Miller MA, Subramanian S, Kaygusuz G, Montgomery K, et al. A landscape

effect in tenosynovial giant-cell tumor from activation of CSF1 expression by a translocation in a minority of tumor cells. Proc Natl Acad Sci USA. 2006;103(3):690-5.
9. Salerno M, Avnet S, Alberghini M, Giunti A, Baldini N. Histogenetic characterization of giant cell tumor of bone. Clin Orthop Relat Res. 2008;466(9):2081-91.
10. Moskovszky L, Szuhai K, Krenács T, Hogendoorn PC, Szendroi M, Benassi MS, et al. Genomic instability in giant cell tumor of bone. A study of 52 cases using DNA ploidy, relocalization FISH, and array-CGH analysis. Genes Chromosome Cancer. 2009;48(6):468-79.
11. Gorunova L, Steyern F, Storlazzi CT, Bjerkehagen B, Follerås G, Heim S, et al. Cytogenetic analysis of 101 giant cell tumors of bone: nonrandom patterns of telomeric associations and other structural aberrations. Gene Chromosome Cancer. 2009;48(7):583-602.
12. Forsyth RG, De Boeck G, Bekaert S, De Meyer T, Taminiau AH, Uyttendaele D, et al. Telomere biology in giant cell tumour of bone. J Pathol. 2008;214(5):555-63.
13. Steyern F, Bauer HC, Trovik C, Kivioja A, Bergh P, Jörgensen P, et al. Treatment of local recurrences of giant cell tumour in long bones after curettage and cementing. A Scandinavian Sarcoma Group study. J Bone Joint Surg Br. 2006;88(4):531-5.
14. Zhen W, Yaotian H, Songjian L, Ge L, Qingliang W. Giant-cell tumour of bone. The long-term results of treatment by curettage and bone graft. J Bone Joint Surg Br. 2004;86(2):212-6.
15. Su YP, Chen WM, Chen TH. Giant-cell tumors of bone: an analysis of 87 cases. Int Orthop. 2004;28(4):239-43.
16. Bertoni F, Bacchini P, Staals EL. Malignancy in giant cell tumor of bone. Cancer. 2003;97(10):2520-9.
17. Rock MG, Sim FH, Unni KK, Witrak GA, Frassica FJ, Schray MF, et al. Secondary malignant giant-cell tumor of bone. Clinicopathological assessment of nineteen patients. J Bone Joint Surg Am. 1986;68(7):1073-9.
18. Brien EW, Mirra JM, Kessler S, Suen M, Ho JK, Yang WT. Benign giant cell tumor of bone with osteosarcomatous transformation ("dedifferentiated" primary malignant GCT): report of two cases. Skeletal Radiol. 1997;26(4):246-55.
19. Hoch B, Inwards C, Sundaram M, Rosenberg AE. Multicentric giant cell tumor of bone. Clinicopathologic analysis of thirty cases. J Bone Joint Surg Am. 2006;88(9):1998-2008.
20. Marui T, Yamamoto T, Yoshihara H, Kurosaka M, Mizuno K, Akamatsu T. De novo malignant transformation of giant cell tumor of bone. Skeletal Radiol. 2001;30(2):104-8.
21. Fletcher CDM, Unni KK, Mertens F. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Sorf Tissue and Bone. Lyon: IARC Press; 2002.
22. Atkins GJ, Haynes DR, Graves SE, Evdokiou A, Hay S, Bouralexis S, et al. Expression of osteoclast differentiation signals by stromal elements of giant cell tumors. J Bone Miner Res. 2000;15(4):640-9.
23. Anract P, De Pinieux G, Cottias P, Pouillart P, Forest M, Tomeno B. Malignant giant-cell tumours of bone. Clinico-pathological types and prognosis: a review of 29 cases. Int Orthop. 1998;22(1):19-26.

Cite this article as: Channappa TS, Shivakumar HB, Jayaram M, Yatish R, Teja S. Malignant transformation of a recurrent giant cell tumor of bone with lung metastasis: a case report. Int J Res Orthop 2023;9:611-5.