www.jmscr.igmpublication.org Impact Factor 3.79
ISSN (e)-2347-176x

IGM Publication Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Benign, Multicentric, Recurrent and Metastasizing Giant Cell Tumor of Bone: Review of Literature with Role of Immunohistochemistry in Determining Prognosis

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Abstract:
Objective: *Giant cell tumor (GCT) represents around 4-5% of all primary bone tumors. The purpose of this article is to report this unusual case of benign metastasizing GCT and simultaneously emphasize on the role of immunomarkers in predicting the aggressive behaviour of such lesions and a brief review of literature along with the proposed management strategies in these patients.*
Case: *We report a rare case of benign GCT in a 24 years old Asian female. Initial presentation of the disease was 9 years back with involvement of lower end of right humerus; development of a multicentric lesion in right 4th metacarpal 2 years after the humerus lesion, and elbow tumor recurrence after 6 years. In all instances en-block tumor resection with bone grafting was performed. Now, the patient presented to us with recurrent tumor at both sites; radiological types 2&3 lesions, local lymphatic involvement and metastatic nodules in bilateral upper pulmonary lobes. Right shoulder disarticulation with biopsy of pulmonary metastases was performed. Histopathology revealed a benign GCT morphology. Immunohistochemistry for Ki67 showed higher expression, while p53 showed negative staining.*
Conclusion: *GCT is still one of the most obscure and intensively examined tumors of bone. Histology does not predict the clinical outcome & few studies have been performed to identify new markers predictive of aggressive behaviour. A relationship between increased proliferative rate (higher Ki67 expression) and possibility of recurrence has been found. Few pilot studies have demonstrated correlation of p53 mutation with local recurrence and malignant transformation.*
Keywords: *GCT, multicentric, recurrence, metastases, Ki67, p53.*

Introduction

GCT is still one of the most obscure and intensively examined tumors of bone. It is a benign but locally aggressive tumor found in the epiphysis of young adults with a closed epiphyseal plate.[1] Nearly 50% cases occur in the region of knee, <5% affect tubular bones of hands and feet.[1]

The incidence of metastasis as well as multicentricity in GCT is low. Very few cases have been reported till date which had a regional lymphatic involvement at the same time as pulmonary involvement. This could suggest the hypothesis of lymphatic metastases being one of the pathways for dissemination of giant cell tumor of bone.

No definite prognostic markers for GCT have been defined till now. Histology does not predict the clinical outcome and neither do the tumor characteristics. [2,3] Researchers continue to search for a reliable marker that could predict the outcome of patients with GCT. Through this case, the authors intend to highlight the role of immunohistochemical markers,viz. p53 & ki67 index, as upcoming factors to satisfy this need.

Case Presentation

A 24 year old Asian female initially presented with complaint of swelling in the lower end of right humerus 9 years back. On investigating, she was diagnosed as a case of benign GCT. She received treatment for the same in the form of en-block tumor resection with ipsilateral fibular grafting, and was subsequently discharged in a satisfactory condition. However, 2 years later, she presented again with a similar swelling in her right 4th metacarpal region. This also turned out to be benign GCT and was treated similarly as en-block tumor resection with free fibular strut grafting for 3rd, 4th & 5th metacarpal, and the patient was discharged. She again presented with recurrence of right elbow tumor, and was treated with tumor mass excision with arthrodesis of elbow joint with fibular strut graft, and fixation with broad DCP with bone graft from head of right radius. This time patient did not come for regular follow up after discharge. Now this patient again presented with swelling around right elbow region with a concurrent swelling in the right hand. These had been present for duration of one year and were increasing in size. The elbow joint swelling extended from mid arm to mid forearm, with a wound m/s 10 cms present over postero-medial aspect. Elbow was fixed at 90 degree flexion. The right hand swelling was involving whole of the hand as well as wrist, with a distal wound and multiple bleeding points. Finger movements were present. On palpation, both the swellings were hard & tender with clearly defined margins. Distal neuro-vascular status was intact. She also had two enlarged right axillary lymphnodes, which on FNAC showed only reactive morphology. Rest of the general and systemic examination was unremarkable. Routine blood investigations were unremarkable.

Radiograph of the right hand showed an expansile lesion of the 4th metacarpal with destruction of 3rd and 5th metacarpal bones (Figure 1a) along with an expansile lytic lesion of the lower end of right humerus (Figure 1b). CT scan showed large heterogeneously enhancing multifocal soft tissue lesion in the right hand, arm around the right elbow and forearm. Lesion was involving the adjacent muscles and subcutaneous planes. Multiple necrotic areas and multiple foci of calcification were noted within the lesion (Figure 2a). Importantly, an incidental finding of metastatic nodules were also noted in bilateral upper lobes of visualized lung parenchyma (Fig 1c). CT findings were suggestive of recurrent giant cell tumour of the lower end of right humerus and right metacarpal bones, with lymphatic metastasis to right forearm and right elbow joint region, with lung metastasis (Fig 2b).

Right shoulder disarticulation with biopsy of pulmonary metastases was performed. Microscopic examination of the primary tumor, recurrent tumor as well as pulmonary metastasis revealed sheets of round to oval polygonal to elongated mononuclear cells mixed with numerous osteoclastic giant cells containing 50-100 nuclei with opened up chromatin and 1-2

nucleoli (Figure 3a). Occasional mitosis of typical type was noted (Figure 3b). Extension of the giant cell lesion to the adjacent skin and soft tissues with reactive bone formation is present (Figure 3c). Hence, a diagnosis of recurrent multicentric benign giant cell tumor of bone with metastasis to bilateral lung fields and regional lymphatic involvement was made. Immunostaining for Ki 67 and p53 was further done. Ki 67 staining showed increased nuclear positivity in >10% of the tumour cells (Figure 4a), while p53 showed negative staining (Figure 4b).

Patient was discharged subsequently in good condition along with an advice for regular follow up. Radiotherapy or chemotherapy was not given.

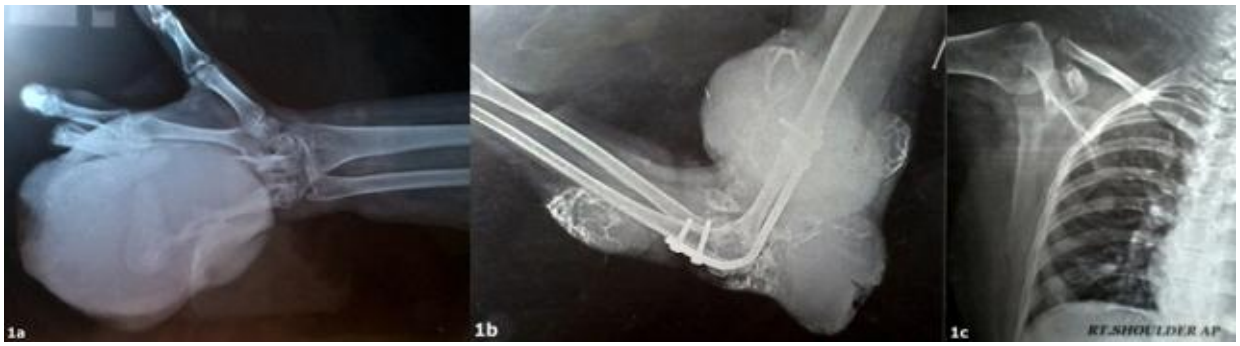

Fig 1a: Radiograph of the right hand showing an expansile lesion of the 4th metacarpal with destruction of 3rd and 5th metacarpal bones.
Fig 1b: Radiograph showing expansile lytic lesion of the lower end of right humerus.
Fig 1c: Chest radiograph showing multiple metastatic nodules.

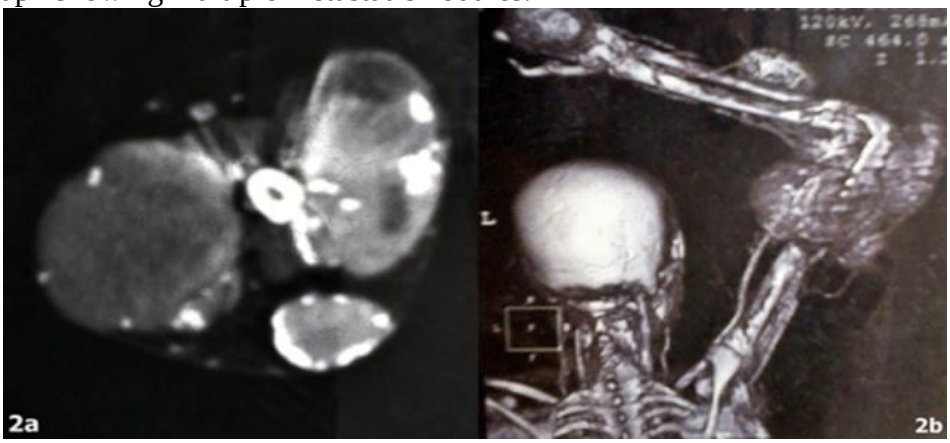

Fig 2a: CT showing multiple necrotic areas and multiple foci of calcification within the lesion.
Fig 2b: CT scan showed large heterogeneously enhancing multifocal soft tissue lesion in the right hand, arm around the right elbow and forearm with lymphatic metastasis.

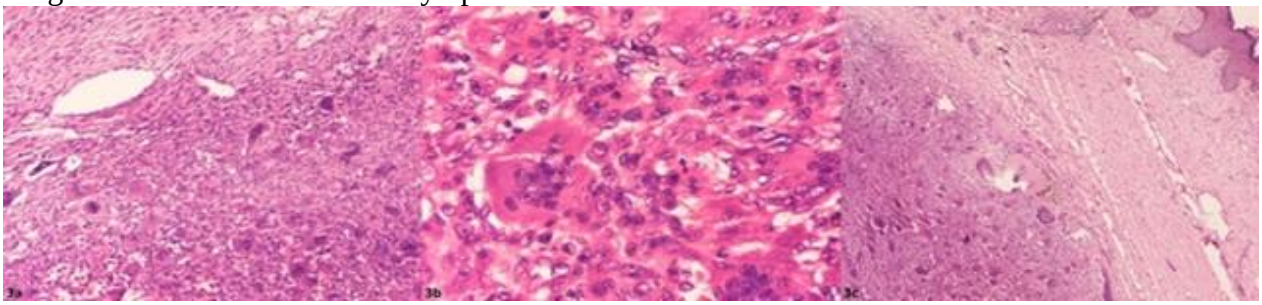

Fig 3a: Photomicrograph of the lesion consisting of sheets of round to oval polygonal to elongated mononuclear cells mixed with numerous osteoclastic giant cells containing 50-100 nuclei with opened up chromatin and 1-2 nucleoli (H &E X 10x).
Fig 3b: High power photomicrograph showing stromal cells with giant cells containing 50-100 nuclei with opened up chromatin and 1-2 nucleoli. Occasional atypical mitoses also seen (H &E X10x).
Fig 3c: Extension of the lesion to the overlying skin and soft tissues with reactive bone formation (H &E X40x).

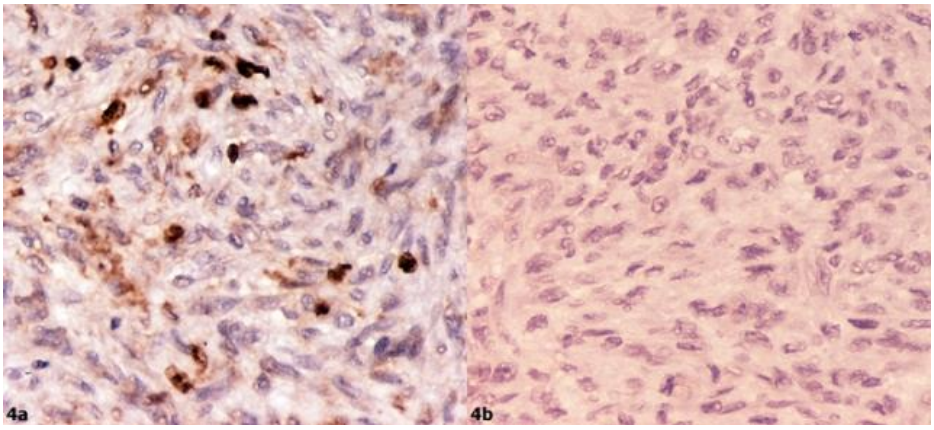

Fig 4a: Ki 67 staining showing increased nuclear positivity in >10% of the tumour cells (IHC Ki67 X 40x).
Fig 4b: Photomicrograph showing negative p53 staining (IHC p53 X 40x).

Discussion

Giant cell tumor of the bone is a locally destructive benign neoplasm occurring in long bones of post pubertal adolescents and young adults where it is found in the epiphysis. Local recurrence occurs in approximately 25% of patients, multicentricity is rare and distant metastases are uncommon. Histologically, they are composed of many large multinucleated giant cells dispersed diffusely among mononuclear cells of benign morphology. They are basically neoplasms of stromal cells that recruit a mononuclear population of haematopoeitic cells.(1) These multinucleated giant cells have been suggested to produce factors that might stimulate the growth of stromal component but this hypothesis is as yet unexplored further.

Various studies have shown minor genomic instabilities in giant cell tumors of bone in vitro.(4-6) These instabilities have been suggested to be the reason behind the low but definite probability of malignant transformation and metastasis clinically. Local recurrence of GCT of bone is quite common with a frequency of 10 to 20%, (7-9) and the probability of recurrence depends on the aggressiveness of the initial surgery.(10) Pulmonary metastasis of benign GCT of bone was first reported by Finch and Gleave in 1926.(11) Since then, it has been reported in an average of 3% of cases (incidence ranging from 2.2 to 4.5% in different studies).(12-14) Other sites of metastasis can be brain, kidney, adrenals, GIT, other bones and skin.(15-21) More than half of the metastasis occurred in patients who also had local recurrence.

Some authors explain the pulmonary lesions as secondary to the tumor emboli often seen in peripheral vessels of GCT due to microvascular trauma during prior surgery and regard the nodules found in the lung as implants and not metastasis.(2,22) Others have not found any correlation between the frequency of detection of tumor emboli in vessels and that of pulmonary involvement.(3,23) We agree with the latter view as seeding of the vessels during curettage cannot explain the simultaneous pulmonary and regional lymph node involvement in our case. Recurrence of the tumor at the earlier site along with dissemination to the lung through the lymphatics explains our case scenario in a better fashion.

Few cases of GCT of bone can undergo malignant transformation also with a varied incidence in various reports. WHO publication, however, mentions the incidence to be 1%.(24)

Giant cell tumor of the bone can have a varied progression with most of the cases having good prognosis. But some cases can have multiple recurrences and pulmonary involvement while still others can have a malignant transformation. Unfortunately till now, no definite prognostic factor has been defined which can predict the patient outcome satisfactorily.

The characteristics of the tumor (including tumor size, localization, surgical stage of the tumor, involvement of subchondral bone or presence of pathological fracture) have not been proven to

have any effect on the prognosis. However, it has been noted in various studies that involvement of the small bones of the hands was associated with a higher risk of recurrence (as was seen in our case also). GCTs of the hand bones have been shown to be more aggressive, associated with an earlier and higher risk of recurrence and are more likely to metastasise to the lungs.[15]

Campanacci et al,[25] developed a classification for GCT based on their radiographic features. The radiographic grade-1 of Campanacci et al, [25] represents a quiescent form, in which the cortical involvement is minimal, if at all. Only 10% to 15% of GCTs belong to this rare stage which can even be asymptomatic. The most common active grade-2 lesions show extensive cortical thinning and bulging. The aggressive grade-3 lesions break through the cortical bone and have a soft tissue component covered by a pseudocapsule and periosteum. On rare occasions, the tumour extends its barrier, the articular cartilage, and enters the joint. This radiological staging system of GCT by Campanacci et al. does not provide reliable prognostic significance in terms of recurrence rates or functional results nor valuable guidelines for decision-making on surgical treatment of GCT.[26]

Tumours and tumour-like lesions containing giant cells with a similar radiographic appearance such as juvenile solitary or aneurysmal bone cysts, chondroblastoma, chondromyxoid fibroma, giant-cell reparative granuloma, nonossifying fibroma, eosinophilic granuloma, high-grade central osteosarcoma should be considered in the differential diagnosis.

Giant cell rich osteosarcoma is an important differential in such cases as they will have a similar presentation with distant metastasis. Hence, it is important to rule out this lesion before considering the possibility of benign metastasizing GCT of bone.

The histological grading has also been found to be of little value and benign histology does not necessarily correlate with the clinical behavior of the tumor.[2,3] Flow cytometry was earlier considered to be a promising prognostic factor but has failed to prove its value.[27,28]

Immunohistochemical examination has come up as a new potential prognostic marker and it has been proven that there is a relationship between the increasing rate of proliferation and the probability of recurrence. The rate of proliferation can be determined through immunohistochemical staining for Ki 67. Few pilot studies have demonstrated the correlation of p53 mutation with local recurrence and malignant transformation. An over expression of p53 was found in GCT metastasizing to lung. [29] In our case, increased nuclear positivity for Ki67 was found in >10% of the tumor cells while p53 was negative. This was similar to the findings of Osaka et al who proved a worse prognosis of patients with increased Ki67 proliferation index,[30] with increased mortality in this group. p53 was not shown to be of much value in their study either.

The overall survival rate of metastasizing GCT has been reported to be 80 to 85%.[31] Sporadically, spontaneous regression of the pulmonary metastasis has also been seen,[32,33] but the overall mortality is 15 to 20%.[32] However, the prognosis becomes poor if the patient develops malignant transformation. The mortality rate in such cases has been found to be 50% despite treatment.[34]

The treatment of choice for the lung nodules is surgical excision.[22,31] In cases where complete excision is not possible, partial excision can suffice. In more advanced cases with unresectable tumors, radiotherapy is recommended.[35] Alternatively, denosumab, which blocks the cytokine receptor activator of nuclear factor-κB ligand (RANKL) may be beneficial,[36] because GCT overexpress RANKL and its receptor.[37]

Because of the varied prognosis of GCT and the lack of a definitive prognostic marker, all cases must be monitored closely for any radiologic or histologic evidence of sarcomatoid transformation. Although radiological follow up with X rays as well as CT scan has been recommended, [32] in resource poor countries like India only X ray follow up should suffice.

Conclusion

Although GCT of bone is a benign lesion and is associated with an overall good prognosis, it has a tendency for local recurrence and distant metastasis (mostly pulmonary) in a small number of cases.

- Before considering the diagnosis of benign metastasizing GCT, the possibility of giant cell rich osteosarcoma should be ruled out as both of them might have a similar presentation
- Ki 67 index and p53 can prove as important prognostic markers for GCT. However, more research is needed in this direction.
- Till the time a definitive prognostic marker can be developed for GCT, regular clinical and radiological follow up seems to be the only method for early diagnosis of recurrence, distant metastasis and malignant transformation of these lesions.

References

1. Werner M. Giant cell tumour of bone: morphological, biological and histogenetical aspects. *Int Orthop*. 2006, 30(6), 484-9. PMID: 17013643.
2. Rock MG, Pritchard DJ, Unni KK. Metastases from histologically benign giant-cell tumor of bone. *J Bone Joint Surg [Am]*. 1984, 66-A, 269-73. PMID: 6693454.
3. Sanerkin NG**.** Malignancy, aggressiveness, and recurrence in giant cell tumor of bone. *Cancer*. 1980, 46, 1641-9. PMID: 7417958.
4. Moskovszky L, Szuhai K, Krenács T, Hogendoorn PC, Szendroi M, Benassi MS, Kopper L, Füle T, Sápi Z. Genomic instability in giant cell tumor of bone. A study of 52 cases using DNA ploidy, relocalization FISH, and array-CGH analysis. *Genes Chromosomes Cancer*. 2009, 48(6), 468-79. PMID: 19242928.
5. Gorunova L, Vult von Steyern F, Storlazzi CT, Bjerkehagen B, Follerås G, Heim S, Mandahl N, Mertens F. Cytogenetic analysis of 101 giant cell tumors of bone: nonrandom patterns of telomeric associations and other structural aberrations. *Genes Chromosomes Cancer*. 2009, 48(7), 583-602. PMID: 19396867.
6. Forsyth RG, De Boeck G, Bekaert S, De Meyer T, Taminiau AH, Uyttendaele D, Roels H, Praet MM, Hogendoorn PC.Telomere biology in giant cell tumour of bone.*J Pathol*. 2008, 214(5), 555-63. PMID: 18278785.
7. Turcotte RE, Wunder JS, Isler MH, Bell RS, Schachar N, Masri BA, Moreau G, Davis AM. Giant cell tumor of long bone: a Canadian Sarcoma Group study. *Clin Orthop Relat Res*. 2002, 397, 248-58. PMID:11953616.
8. Vult von Steyern F, Bauer HC, Trovik C, Kivioja A, Bergh P, Holmberg Jörgensen P, Follerås G, Rydholm A. 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. PMID: 16567792.
9. 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. PMID: 15046435.
10. Su YP, Chen WM, Chen TH. Giant-cell tumors of bone: an analysis of 87 cases. *Int Orthop*. 2004, 28(4), 239-43. PMID: 15160253.
11. Finch, E.F., and Gleave, HH. A case of osteoclastoma (myeloid sarcoma, benign giant cell tumour) with pulmonary metastasis. *J. Pathol. Bacteri. 1926*, 29, 399. DOI: 10.1002/path.1700290408.
12. Balke , Schremper L, Gebert C, Ahrens H, Streitbuerger A, Koehler G, Hardes J, Gosheger G. Giant cell tumour of bone: treatment and outcome of 214 cases. *J*

Cancer Res Clin Oncol. 2008, 134(9), 969-78. PMID: 18322700.

13. Dominkus M, Ruggieri P, Bertoni F, Briccoli A, Picci P, Rocca M, Mercuri M. Histologically verified lung metastases in benign giant cell tumours–14 cases from a single institution. *Int Orthop*. 2006, 30(6), 499-504. PMID: 16909252.
14. Viswanathan S, Jambhekar NA. Metastatic giant cell tumor of bone: are there associated factors and best treatment modalities?. *Clin Orthop Relat ReS*. 2010, 468(3),827-33. PMID: 19597900.
15. Averill, R. M., Smith, R. J., and Campbell, C. J. Giant-cell tumors of the bones of the hand. *J. Hand Surg.* 1980, 5A,39. PMID: 7365216.
16. Campanacci, M.: Bone and soft tissue tumors. *New York, Springer-Verlag Wien*. 1990,117-151.
17. Dyke SC. Metastasis of the "benign" giant cell tumor of bone (osteoclastoma). *J. Pathol. Bacteriol*. 1931, 34,259. DOI: 10.1002/path.1700340212.
18. Goldenberg, R. R., Campbell, C. J., and Bonfiglio M. Giant-cell tumor of bone: An analysis of two hundred and eighteen cases. *J. Bone Joint Surg Am*. 1970 Jun;52(4):619-64. PMID: 5479455.
19. Scott, S. M., Pritchard, D. J., Unni, K. K., Rainwater,L. M., and Lieber, M. M. "Benign" metastasizing giant-cell tumor: Evaluation of nuclear DNA patterns by flow cytometry. *J. Orthop. Res*. 1989, 7(4):463-7. PMID: 2738764.
20. Szyfelbein, W. M., and Schiller, A. L. Cytologic diagnosis of giant cell tumor of bone metastatic to lung: A case report. *Acta. Cytol*. 1979, 23, 460-464. PMID: 295163.
21. Tubbs WS, Brown LR, Beabout JW, Rock MG, Unni KK. Benign giant-cell tumor of bone with pulmonary metastases: clinical findings and radiological appearance of metastases of 13 cases. *AJR Am J Roentgenol*. 1992, 158,331-4. PMID: 1729794.
22. Bertoni F, Present D, Enneking WF. Giant-cell tumour of bone with pulmonary metastases. *J Bone Joint Surg [Am]*.1985, 67-A, 890-900. PMID: 4019539.
23. .Maloney WF, Vangham LM, Jones HH, Ross J, Nagel DA . Benign metastasizing giant-cell tumor of bone: report of three cases and review of the literature. *Clin Orthop*. 1989, 243,208-15. PMID: 2656024.
24. Fletcher CDM, Unni KK, Mertens F, (eds.): World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Soft Tissue and Bone IARC Press, Lyon 2002.
25. Campanacci M, Giunti A, Olmi R. Giant-cell tumours of bone: a study of 209 cases with long term follow up in 130 cases. *Ital J Orthop Traumatol*. 1975, 1,249-77.
26. Wang H, Wan N, Hu Y. Giant cell tumor of bone: a new evaluating system is necessary. *Int Orthop*. 2012, 36(12), 2521–2527. PMID: 23052276.
27. Fukunaga M, Nikaido T, Shimoda T, Ushigome S, Nakamori. A flow cytometric DNA analysis of giant cell tumors of bone including two cases with malignant transformation.*Cancer*. 1990, 70,1886-94. PMID: 1525763.
28. Krober SM, Greschniok A, Bohm P, Kaiserling E. Giant cell tumor of bone: morphological, immunohistochemical, morphometric and DNA flow-cytometric findings. *Verh Dtsch Ges Pathol*. 1998, 82, 279-83. PMID: 10095447.
29. M. Szendroi . Giant cell tumour of bone: Review. *Journal of bone and joint surgery [Br]*. 2004, 86-B, 5-12. PMID: 14765857.
30. Osaka S et al. Clinical and immunohistochemical characteristics of benign giant cell tumor of bone with pulmonary metastasis: case series. *Journal of orthopaedic surgery*. 2004, 12(1), 55-62. PMID: 15237123.

31. Cheng JC, Johnston JO. Giant-cell tumor of bone: prognosis and treatment of pulmonary metastases. *Clin Orthop*. 1997, 338, 205-14. PMID: 9170381.
32. Siebenrock KA, Unni KK, Rock MG. Giant cell tumor of bone metastasizing to the lungs: a long-term follow-up. *J Bone Joint Surg [Br]*. 1998, 80-B,43-47. PMID: 9460951.
33. Kay RM, Eckhardt JJ, Seeger LL, Mirra JM, Hok DJ . Pulmonary metastasis of benign giant cell tumor of bone: six histologically confirmed cases, including one of spontaneous regression. *Clin Orthop*. 1994, 302,219-30. PMID: 8168305.
34. Anract P, De-Piueus G, Cottias P, Pouillart P, Forest M, Tomeno B. Malignant giant-cell tumor of bone: clinical-pathological types and prognosis: a review of 29 cases. *Int Orthop*. 1998, 22,19-26. PMID: 9549577.
35. Feigenberg SJ, Marcus RB, Zlotecki RA, Scarborough MT, Enneking WF. Whole-lung radiotherapy for giant cell tumors of bone with pulmonary metastases. *Clin Orthop*. 2002, 401, 202-8. PMID: 12151897.
36. Thomas D , Henshaw R , Skubitz K , Chawla S , Staddon A , Blay JY , Roudier M, Smith J , Ye Z , Sohn W , Dansey R , Jun S . Denosumab in patients with giant-cell tumour of bone: an open label, phase 2 study. *Lancet Oncol . 2010,* 11,275–280. PMID: 20149736.
37. Atkins , Haynes DR , Graves SE , Evdokiou A , Hay S , Bouralexis S , Findlay DM. Expression of osteoclast differentiation signals by stromal elements of giant cell tumors. *J Bone Miner Res*. 2000, 15, 640–649. PMID: 10780856.