

Metastatic Giant Cell Tumor of Bone: A Case Report

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Abstract

Giant cell tumor of bone is a relatively rare primary bone neoplasm. It was originally classified as benign tumor; however, it rarely presents as aggressive disease with the potential to distant metastasis mainly in lung. The objective of this study was to present and discuss a case of metastatic giant cell tumor. A young female patient with a recent history of resected bone lesion, hospitalized with dyspnea, was investigated and extensive lung metastasis was found. She received one cycle of chemotherapy until availability of molecular targeted therapy; however, she died due to disease complications 1 day after introduction of denosumab. This rare neoplasm is slightly predominant in females, typically occurring during the third or fourth decades of life, when bone maturity is reached. Accurate diagnosis is given by histopathological analysis. Microscopically the neoplasm is characterized by the presence of multinucleated giant cells of osteoclast type amid a richly vascular stroma of mononuclear cells. The standard treatment is curettage, filling with cement (polymethylmethacrylate) or bone graft. The possibility of recurrence is significant, and 15-50% of cases are treated with simple curettage. In cases where surgery is not possible, the systemic treatment can be attempted. The choice of the treatment regimen is based on case reports or series of cases. Recently a promising targeted therapy emerged, denosumab, a monoclonal antibody directed to the RANK ligand-L. In our case, besides the severity of the disease, inadequate follow-up after surgery and delayed access to specialized services may have contributed to the outcome.

Keywords: Sarcoma; Giant cell; Metastatic; Chemotherapy

Introduction

The giant cell tumor of bone (GCTB) is a relatively rare primary bone neoplasm. It represents about 5% of primary bone tumors and accounts for about 20% of bone benign neoplasms [1, 2]. GCTB is classified as benign; however, some case reports describe aggressive forms of the disease with metastatic potential, most often to the lungs [3].

Around 60% of the cases of GCTB affect women, with 70-80% of them typically during the third or fourth decades of life, when skeletal maturity is reached [3-5].

Historically the GCTB was first described in 1818 by Cooper and Travers; Nelaton deepened into its clinical features in 1860, but only in 1912 Bloodgood used the name “giant cell tumor” and employed local curettage and bone grafting as treatment, preventing member amputation as widely practiced until then [4, 6-8].

Systemic therapy is reserved to cases when surgery cannot be performed and it is based on few case reports. This is a case report study to report the experience of the Hospital Sao Paulo (University Hospital - UH/Universidade Federal de Sao Paulo - UNIFESP) in the treatment of a case of metastatic GCTB.

Case Report

The patient was a 24-year-old female with a history of childhood asthma and no bronchospasm for many years. She had history of surgery for bone tumor in the distal region of the right tibia 8 months before admission in Hospital Sao Paulo; however, the material was not sent for histopathological analysis. Whole body computed tomography (CT) was not performed at that time.

About 3 months after orthopedic surgery, the patient begins with history of progressive dyspnea and 5 months later arrived in Hospital Sao Paulo.

She underwent investigation by clinical examination that revealed dyspnea without inflammatory or infectious characteristic and distal tibia bulging. Imaging studies were performed with chest radiograph (Fig. 1), CT of the leg (Fig. 2) and skeletal scintigraphy (Fig. 3).

Cytological research was also carried out by bronchoscopy with transbronchial biopsy and biopsy of the tibial lesion.

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Figure 1. Chest radiograph showing multiple implants in the lungs.

The biopsies confirmed the diagnosis of giant cell tumor in both materials.

We opted for systemic therapy because of irresectability of pulmonary lesions; however, before starting systemic therapy, the patient developed sudden worsening of dyspnea by spontaneous right pneumothorax (Fig. 4).

After resolution of clinical complication, she started systemic treatment with cisplatin 25 mg/m² and doxorubicin 25 mg/m² on day 1 and day 2. Three days after the first cycle of chemotherapy, she developed respiratory failure and required mechanical ventilation with exclusion of infectious etiology. After a week in the intensive care unit, denosumab was made available by the board of the Hospital Sao Paulo in view of the severity of the case. Subcutaneously 120 mg was administered on the 10th day after the start of chemotherapy. However, the patient remained respiratory complications and died the day after receiving denosumab.

Discussion

The GCTB is rare bone neoplasm primarily classified as benign; however, disseminated disease was described, most often to the lungs [3]. GCTB usually begins in the epiphysis of long bones and tends to expand into the metaphysis or the joint compartment [5, 8].

The most common symptom in the early stage of the disease is localized pain combined with a visible or palpable mass, sometimes with rapid growth [4, 5, 8]. The most involved sites in decreasing order of frequency are the distal femur, proximal tibia, proximal femur, distal radius and distal tibia [4, 5].

Lungs are the main metastatic site, and the recurrence of bone disease increases the risk of distant implants; approximately 5% of these recurrent cases develop lung disease [4, 9, 10]. Multicenter disease at the diagnosis, as described above, is a very rare condition, affecting less than 1% of the patients [2].

Radiologically the GCTB presents itself initially as a lytic lesion without sclerotic margin, eccentric, within the limits of



Figure 2. Right leg radiography showing bone changes in the distal tibia.

cortical. As it grows, it becomes insuflative, with a wide transition zone, thinned bone cortex, extensive remodeling and invasion of metaphyseal bone, involving the whole bone diameter, disrupting the cortical, provoking pathological fracture and compromising the adjacent soft tissues [4].

Accurate diagnosis is given by histopathological analysis by punch biopsy or local resection. Differential diagnoses include brown tumor of hyperparathyroidism, aneurysmal bone cyst, osteogenic sarcoma, chondroblastoma and fibrosarcoma [1, 5, 8, 11].

The histogenesis of GCTB is still obscure, without any identified correlation between the histological grade at presentation and tumor aggressiveness. It is assumed that giant cells are monocytes transformed into osteoclasts that express RANKL (kappa B nuclear factor receptor), an essential growth factor in the osteoclastic differentiation and activation [4, 5, 10, 12].

Over the past 30 years, the GCTB, specially the localized form, has been treated with intralesional curettage, cement (polymethylmethacrylate) filling or bone graft and, alternatively, with segmental resection of the lesion with surgical margins [4, 5, 9, 12].

The possibility of local recurrence is significant, reaching 15-50% of the cases treated with local curettage [5]. When it occurs, 75% of them appear within the first 2 years of the follow-up [13]. The use of chemical and thermal adjuvants, such as phenol, hydrogen peroxide and liquid nitrogen, reduced the recurrence rate to 17%, getting lower when cavity filling with cement was performed [8, 9, 12, 14, 15]. Wide *en bloc*

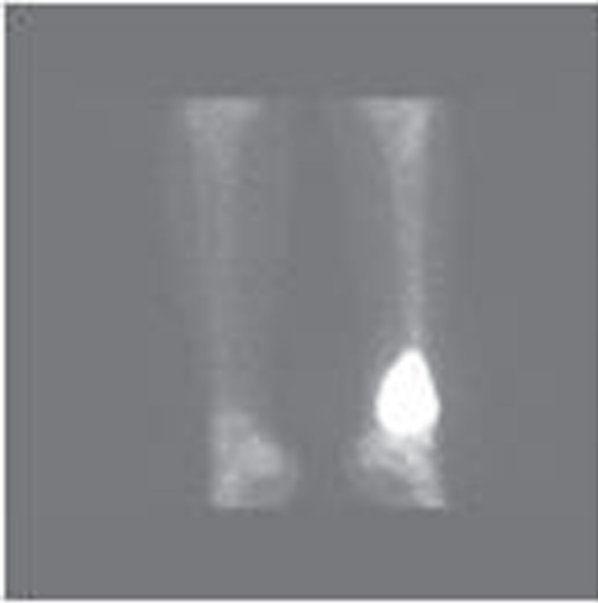


Figure 3. Skeletal scintigraphy showing uptake in the distal tibia.

resections promote greater control of the disease and lower recurrence rates of about 5%; however, there is a higher rate of surgical complications, present in 16% of the cases, and functional impairment [1, 3-5].

Radiotherapy presents a local control rate of the disease of 60-84%; however, due to the risk of sarcomatous degeneration, described in up to 11% in some series of cases, this treatment modality is reserved for cases with lesions unable to be removed with surgical margins, like those located in sacrum [4, 5, 8, 10, 12, 15].

Even for metastatic disease, the surgical resection remains the treatment of choice. In cases where surgery is not possible because of the patient's adverse condition or disease itself, systemic treatment can be used. The choice of systemic treatment regimen is made based on small studies reports or series of cases. No prospective studies have evaluated the chemotherapeutic treatment of GCTB. The agents most commonly reported are ifosfamide, cyclophosphamide, doxorubicin and cisplatin in various combinations. Interferon is described for the treatment of aggressive GCTB; however, this drug is associated with several potentially serious adverse effects, remaining currently as an option after the failure of surgery, radiotherapy and targeted molecular therapy [8].

Recently a promising new treatment option with molecular targeted therapy has emerged, the denosumab, a monoclonal antibody directed to the RANK ligand-L, preventing it from binding to the receptor of nuclear factor kappa-B and interrupting the osteoclast differentiation and activity. A small phase 2 study with 35 patients showed a 86% rate activity against the disease with up to 65% reconstitution of cortical [16]. However, it is not available for use in the Brazilian public health system.

In the current case report, it was decided for the use of conventional chemotherapy regimen with cisplatin and doxorubicin, described by another report in which a single patient

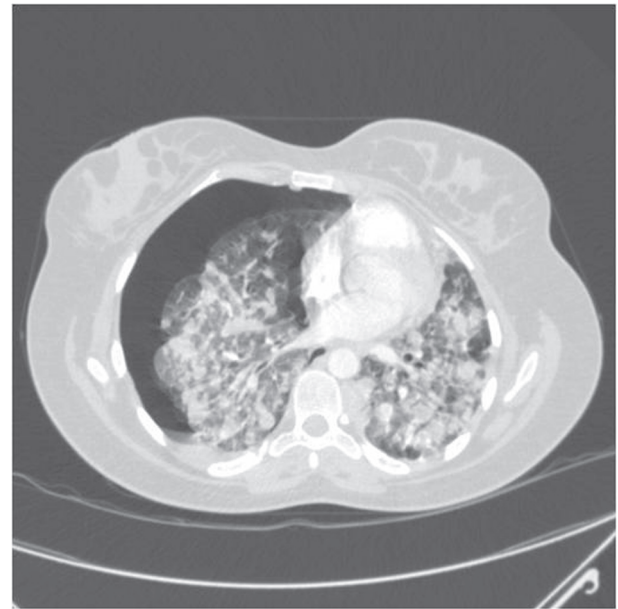


Figure 4. Computed tomography of the chest showing pneumothorax and multiple implants in the lungs.

had been submitted to surgery and adjuvant chemotherapy, achieving prolonged disease control [17]. Interferon would be a plausible drug, but it was not available in our service. After the end of the first chemotherapy cycle, the patient received one application of denosumab, but she died of lung metastases complications after just 1 day, without possibility of experiencing the benefits of treatment.

Conclusion

GCTB is rare neoplasm with unpredictable behavior considering its histopathological analysis. The main treatment is still based on intralesional curettage associated or not with cement filling or bone graft, leaving the systemic therapy options for cases where surgery is not feasible. The prognosis depends mainly on the behavior of the disease, since there are no prognostic markers for this tumor.

Conflicts of Interest

There are not any conflicts of interest.

References

1. Radulescu R, Badila A, Nutiu O, Manolescu R, Ciobanu T, Sajin M, Japie IM. Giant-cell tumor of the bone (GCTOB): clinical case. *Rom J Morphol Embryol.* 2013;54(2):433-436.
2. Shekhar A, Murgod G, Korhalli S. Synchronous Multi-centric Giant Cell Tumour (GCT)-A Rare Case Report. *J Clin Diagn Res.* 2014;8(2):185-186.

3. Wang H, Wan N, Hu Y. Giant cell tumour of bone: a new evaluating system is necessary. *Int Orthop*. 2012;36(12):2521-2527.
4. Amanatullah DF, Clark TR, Lopez MJ, Borys D, Taurian RM. Giant cell tumor of bone. *Orthopedics*. 2014;37(2):112-120.
5. Szendroi M. Giant-cell tumour of bone. *J Bone Joint Surg Br*. 2004;86(1):5-12.
6. Bloodgood JC. II. The Conservative Treatment of Giant-Cell Sarcoma, with the Study of Bone Transplantation. *Ann Surg*. 1912;56(2):210-239.
7. McCarthy EF. Giant-cell tumor of bone: an historical perspective. *Clin Orthop Relat Res*. 1980;153:14-25.
8. Camargo OP, Croci AT, Oliveira CR, Baptista AM, Gianotti MA. Tumor de celulas gigantes - evolucao historica do seu diagnostico e tratamento junto ao Instituto de Ortopedia e Traumatologia da FMUSP. *Acta Ortop Bras*. 2001;9(6):7.
9. Klenke FM, Wenger DE, Inwards CY, Rose PS, Sim FH. Giant cell tumor of bone: risk factors for recurrence. *Clin Orthop Relat Res*. 2011;469(2):591-599.
10. Miller IJ, Blank A, Yin SM, McNickle A, Gray R, Gitelis S. A case of recurrent giant cell tumor of bone with malignant transformation and benign pulmonary metastases. *Diagn Pathol*. 2010;5:62.
11. Haque AU, Moatasim A. Giant cell tumor of bone: a neoplasm or a reactive condition? *Int J Clin Exp Pathol*. 2008;1(6):489-501.
12. Kim Y, Nizami S, Goto H, Lee FY. Modern interpretation of giant cell tumor of bone: predominantly osteoclastogenic stromal tumor. *Clin Orthop Surg*. 2012;4(2):107-116.
13. Goldenberg RR, Campbell CJ, Bonfiglio M. Giant-cell tumor of bone. An analysis of two hundred and eighteen cases. *J Bone Joint Surg Am*. 1970;52(4):619-664.
14. Camargo OP. O estado de arte no diagnostico e tratamento do tumor de celulas gigantes do osso. *Rev Bras Ortop*. 2002;6.
15. Drumond JM. Tumores osseos benignos e lesoes osseas pseudotumorais: tratamento atual e novas tendencias. *Rev Bras Ortop*. 2009;44(5):5.
16. Branstetter DG, Nelson SD, Manivel JC, Blay JY, Chawla S, Thomas DM, Jun S, et al. Denosumab induces tumor reduction and bone formation in patients with giant-cell tumor of bone. *Clin Cancer Res*. 2012;18(16):4415-4424.
17. Stewart DJ, Belanger R, Benjamin RS. Prolonged disease-free survival following surgical debulking and high-dose cisplatin/doxorubicin in a patient with bulky metastases from giant cell tumor of bone refractory to "standard" chemotherapy. *Am J Clin Oncol*. 1995;18(2):144-148.