Multiple Pulmonary Metastases of Giant Cell Tumor of Bone with expression of VEGFR-2 Successfully Treated by Denosumab and Apatinib: A Rare Case Report

taojun gong
Sichuan University West China Hospital

Yi Luo
Sichuan University West China Hospital

Yitian Wang
Sichuan University West China Hospital

Chuanxi Zheng
Sichuan University West China Hospital

Jianguo Fang
Sichuan University West China Hospital

Li Min
Sichuan University West China Hospital

Yong Zhou
Sichuan University West China Hospital

Chongqi Tu (✉ tuchongqibone@hotmail.com)
Sichuan University West China Hospital

Case report

Keywords: Giant cell tumor of bone, Pulmonary metastasis, VEGFR-2, Denosumab, Apatinib

DOI: https://doi.org/10.21203/rs.3.rs-221200/v1

License: © This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Abstract

**Background:** Giant cell tumor of bone (GCTB) is a rare benign but locally aggressive bone tumor. It has a high tendency for local recurrence, which may increase the occurrence of lung metastasis. Currently, the treatment of pulmonary metastases of GCTB is controversial. Denosumab is the preferred regimen for unresectable metastatic lesions, but there are no alternative treatment options when denosumab is resistant. So far, no case reports of metastatic GCTB treated with denosumab and apatinib have been published.

**Case presentation:** This is a case report of a 26-year-old female who experienced right knee pain for over 6 months. Radiography and computed tomography revealed osteolytic bony destruction in the proximal right tibia. Using histological, radiological, and clinical techniques, a diagnosis of GCTB was achieved. Meanwhile, the immunohistochemical stain-identified the tumor cells were positive for vascular endothelial growth factor receptor 2 (VEGFR-2). After intralesional curettage of the primary tumor and wide resection of local recurrence surgeries, she developed recurrent hemoptysis. Chest computed tomography (CT) images showed multiple pulmonary nodules. She was administrated denosumab therapy but disease progression was confirmed after four months of treatment. She then received denosumab and apatinib therapy for 24 months, after a partial response was achieved.

**Conclusions:** We depict a case of multiple pulmonary metastases of GCTB successfully controlled by denosumab and apatinib therapy. VEGFR-2 may be an effective therapeutic target for GCTB with pulmonary metastasis when denosumab is ineffective.

Introduction

Giant cell tumor of bone (GCTB) is a rare benign but locally aggressive bone tumor, accounting for 3%~5% of all primary bone tumors [1]. This tumor typically occurs at the age of 20–40, generally more common in females [2], and has a high tendency for local recurrence [1, 3]. Pulmonary metastasis rarely occurs in 1-3.9% in patients without local recurrence and 6-21.1% in patients with local recurrence. The overall mortality rate of these patients varied widely from 0 to 23% [4].

GCTB has been demonstrated to positively express receptor activator of nuclear factor κB ligand (RANKL), which was specifically blocked by denosumab. Denosumab is a fully human monoclonal antibody against RANKL, inhibiting osteoclast-like giant cells and their precursors. This inhibition leads to a reduction or elimination of giant cells, inhibition of osteolysis, and subsequent replacement with dense, new bone [5]. In 2013 the Food and Drug Administration approved the application of denosumab in the local disease of adults and skeletally mature children with unresectable GCTB or surgical resection may result in severe morbidity [6]. Meanwhile, denosumab is an option for patients with unresectable metastases. For patients presenting with resectable metastases, surgical is recommended. However, there are no alternative treatment options when denosumab is resistant. Here, we present a patient with
pulmonary metastatic GCTB who initially resisted denosumab treatment and then effectively treated by a combination of denosumab and apatinib.

Case Presentation

A 26-year-old female was referred to our hospital in June 2014 with a complaint of dull pain in the right knee for six months. Physical examination showed swelling and tenderness in the right tibia. Radiography and computed tomography (CT) revealed an eccentric, well-defined lytic lesion with cortical destruction in the proximal metaphysis of the right tibia, suggesting the diagnosis of GCTB (Fig. 1) (Campanacci grade III). Chest CT (Fig. 4) and single-photon emission computed tomography (Fig. 1) did not reveal any metastatic lesions. An incisional biopsy was performed, pathological findings confirmed the diagnosis of GCTB (Fig. 3). Subsequently, the patient underwent intralesional curettage of the lesion in the right tibia and was reconstructed with cement. However, nine months later, a soft tissue mass was found in the right popliteal fossa. CT and magnetic resonance imaging (MRI) revealed lytic lesions around the cement with soft tissue extension (Fig. 2) and the CT scan of the chest still did not show any metastatic lesions. Because of the extensive recurrence, the patient underwent wide resection of the lesion in the right tibia with prosthetic reconstruction. The pathological findings microscopically revealed recurrence of GCTB and immunohistochemical stain-identified the tumor cells were positive for VEGFR-2, P63, and MIB1 (Fig. 3). The patient was regularly followed-up every three months for three years in our orthopedic clinic with a satisfactory postoperative function of the right knee.

Unfortunately, two years after the second surgery, the patient presented to our clinic with a complaint of hemoptysis. Chest CT identified the multiple pulmonary nodules in the bilateral lung (Fig. 4). Although the biopsy of the lung mass was not performed owing to the refusal of the patient, the metastatic lesions of GCTB were considered by the radiological progression in the subsequent one-month follow-up. Given the advanced metastatic disease and infeasibility of surgical excision, the patient chose the subcutaneous denosumab administration which was initiated at a dose of 120 mg every 28 days, with additional doses on days 8 and 15 of the first month and then repeated monthly. Simultaneously, the patient also supplements the calcium and vitamin D. However, after four months, the symptoms of hemoptysis became more severe. The CT scan of the chest showed the lung metastatic nodules increased in size and number, indicating the progression of disease (Fig. 4). After the multiple disciplinary team discussions, the patient was tentatively administrated the tyrosine kinase inhibitor, apatinib, in combination with denosumab treatment. Denosumab was injected every month with a dose of 120 mg and apatinib was administered with a dose of 500 mg daily. After three months of denosumab and apatinib treatment, the symptom of hemoptysis was alleviated. Importantly, the chest CT showed the tumor size of the largest lung nodule was reduced greatly, and there was no other new lesion developed (Fig. 1). After 36 months of follow-up, the largest one had greatly decreased in size from 12.20 x 8.52 cm to 3.46 x 1.54 cm, and there were no new measurable nodules (Fig. 4). The patient showed a partial response (PR) to denosumab and apatinib treatment by RECIST 1.1. During the treatment of apatinib, several drug-related adverse events occurred, including gastrointestinal discomfort, hypopigmentation of the hair, fatigue, hand-foot skin syndrome. These adverse events were effectively remitted by symptomatic treatments.
Discussion

Although GCTB was classified as a benign tumor, the lung metastases rate differed from 1-21.1% and show a rising trend recently [3, 4]. Currently, the treatment of pulmonary metastasis for GCTB patients is still controversial. According to the National Comprehensive Cancer Network (NCCN) guidelines, surgical excision is the mainstay of the treatment for patients with resectable metastases. Denosumab therapy is a recommended regimen for patients with unresectable metastatic lesions [1, 5, 7]. Other alternatives include interferon alfa-2b, radiation therapy, or observation. However, interferon therapy had limited efficacy to treat metastases in most patients, and radiation therapy may increase the risk of malignant transformation.

The role of denosumab in controlling unresectable (local or metastatic) tumors has been well established [1, 5]. Luo et al reported seven patients with pulmonary metastatic GCTB who received denosumab treatment. None of their patients with metastatic disease progression was found during an average of 28.6 months follow-up period. Three patients showed partial response and four patients got stable disease after denosumab treatment [8]. An open-label, phase II study divided GCTB patients into 3 cohorts. Cohort 1 incorporated 169 patients including 43 pulmonary diseases with unresectable GCTB treated with denosumab. After a median follow-up of 13 months, 96% (163 of 169) of evaluable patients had no disease progression [9]. However, they also mentioned that six unresectable GCTB cases were determined to have disease progression after denosumab therapy, only one patient who had radiological progression continued denosumab therapy because of a good clinic response, one died of pulmonary complications, the other four stopped denosumab treatment, whereas the subsequent therapy was not documented.

In the presented case, denosumab alone was invalid in managing pulmonary metastases and the disease progressed after four months of denosumab therapy. As specimens of lung metastases were not available, it is hard to determine the pathological features of the metastatic lesions. We speculate whether the pathological changes had occurred in the metastatic lesions according to the rapid radiological progression despite previous literature indicated that pulmonary metastatic tumors maintained benign histological features [10]. In other words, if denosumab is still effective in malignant or sarcomatous GCTB. At the same time, the immunohistochemistry result of the recurrence in the patient was positive for VEGFR-2, indicating the antiangiogenetic therapy might be the potential therapeutic targets. As denosumab seems invalid to control the pulmonary metastases, but a cessation of denosumab therapy might lead to local recurrence of the tumor and critical hypercalcemia [11, 12], therefore, we decided to tentatively treat the patient with apatinib but did not rule out the denosumab treatment completely.

Pathological angiogenesis has been demonstrated to be a key role in the progression, invasion, and metastasis of tumor cells. Vascular endothelial growth factor (VEGF), overexpressed in many solid tumors including GCTB, is one of the central triggers for angiogenesis[13, 14]. VEGFR-2 presenting a strong tyrosine kinase activity towards pro-angiogenic signals is the key mediator of recognized VEGF
induced phenotypes [15]. Most anti-angiogenic therapy in treating tumors mainly targets the VEGF-VEGFR system so far. Apatinib is a novel tyrosine kinase inhibitor (TKI) that selectively competes for VEGFR-2 ATP binding site, blocking downstream signaling and inhibiting tumor angiogenesis [16]. This therapy is effective for a wide range of primary malignancies and metastatic lesions, such as advanced gastric cancer, osteosarcoma, rhabdomyosarcoma, synovial sarcoma, and alveolar soft part sarcoma [17–19]. Wang et al showed a satisfactory result of the application of apatinib in 6 cases of pulmonary metastatic alveolar soft part sarcoma, leading to one complete response and five PRs [19]. Zhu et al reported an objective response rate of 33.3% and clinical benefit rate of 75.0% when apatinib was administered for 31 advanced sarcoma patients including 18 pulmonary metastases [18]. To our knowledge, there were limited reports discussed the efficiency of TKI and denosumab in the treatment of GCTB. Wang, G et al presented a case of GCTB with pulmonary and bone metastases that were treated with denosumab and sunitinib, and their patient achieved stable disease after four years of treatment [20]. Li, J et al reported a multicentric GCTB patient treated with apatinib and CT in the fourth month identified a partial response [21]. However, no study has previously used denosumab and apatinib for pulmonary metastases of GCTB.

In summary, when denosumab was invalid, the treatment strategy was unclear for patients with multiple pulmonary GCTB metastases. VEGFR-2 may provide an effective therapeutic target. We have shown that the novel combination of denosumab and apatinib can be used to treat pulmonary metastatic GCTB. However, long-term safety and the optimal duration of this therapy are still to be determined.

**Abbreviations**

GCTB: Giant cell tumor of bone; CT: Computed tomography; PR: Partial response; VEGF: Vascular endothelial growth factor; VEGFR-2: Vascular endothelial growth factor receptor 2; TKI: Tyrosine kinase inhibitor; RECIST: Response Evaluation Criteria for Solid Tumors; SPECT: Single-photon emission computed tomography; MRI: Magnetic resonance imaging; NCCN: National comprehensive cancer network; RANKL: nuclear factor κB ligand; PD: Progressive disease; CR: complete response; HFS: Hand-foot skin syndrome.

**Declarations**

**Ethics approval and consent to participate**

Informed written consent was obtained from the patient for publication of this case report and accompanying images.

**Consent for publication**

The written consent to publish images or other personal or clinical details of participants was obtained from the patient.
Availability of data and materials

All data used or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported, in part, by the Chengdu Science and Technology Program Projects (No. 2017-CY02-00032-GX, Dr. Zhou) and the National Natural Science Foundation of China (No. 81801852, Dr. Zhou), the National Key Research and Development Program of China (No. 2017YFB0702604, Dr. Min).

Authors’ contributions

All authors participated in the management of the patient in this case report. TJG collected the data and drafted the manuscript. ML, YZ, YL collected and analyzed the data. YTW, CXZ, JGF designed, supervised the report of the manuscript. CQT critically revised the manuscript. All authors read and approved the manuscript.

Acknowledgments

Not Applicable.

References

1. Thomas D, Henshaw R, Skubitz K, Chawla S, Staddon A, Blay JY, Roudier M, Smith J, Ye Z, Sohn W, et al. Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study. The Lancet Oncology. 2010;11(3):275–80.

2. Mendenhall WM, Zlotecki RA, Scarborough MT, Gibbs CP, Mendenhall NP. Giant cell tumor of bone. Am J Clin Oncol. 2006;29(1):96–9.

3. Wang J, Liu X, Yang Y, Yang R, Tang X, Yan T, Guo W: Pulmonary metastasis of giant cell tumour: a retrospective study of three hundred and ten cases. International orthopaedics 2021.

4. Bertoni F, Present D, Sudanese A, Baldini N, Bacchini P, Campanacci M. Giant-cell tumor of bone with pulmonary metastases. Six case reports and a review of the literature. Clinical orthopaedics and related research 1988(237):275–285.
5. Chawla S, Blay JY, Rutkowski P, Le Cesne A, Reichardt P, Gelderblom H, Grimer RJ, Choy E, Skubitz K, Seeger L, et al. Denosumab in patients with giant-cell tumour of bone: a multicentre, open-label, phase 2 study. The Lancet Oncology. 2019;20(12):1719–29.

6. Balke M. Denosumab treatment of giant cell tumour of bone. The Lancet Oncology. 2013;14(9):801–2.

7. Biermann JS, Chow W, Reed DR, Lucas D, Adkins DR, Agulnik M, Benjamin RS, Brigman B, Budd GT, Curry WT, et al: NCCN Guidelines Insights: Bone Cancer, Version 2.2017. Journal of the National Comprehensive Cancer Network: JNCCN 2017, 15(2):155–167.

8. Luo Y, Tang F, Wang Y, Zhou Y, Min L, Zhang W, Shi R, Duan H, Tu C. Safety and efficacy of denosumab in the treatment of pulmonary metastatic giant cell tumor of bone. Cancer management research. 2018;10:1901–6.

9. Chawla S, Henshaw R, Seeger L, Choy E, Blay JY, Ferrari S, Kroep J, Grimer R, Reichardt P, Rutkowski P, et al. Safety and efficacy of denosumab for adults and skeletally mature adolescents with giant cell tumour of bone: interim analysis of an open-label, parallel-group, phase 2 study. The Lancet Oncology. 2013;14(9):901–8.

10. Hoch B, Inwards C, Sundaram M, Rosenberg AE. Multicentric giant cell tumor of bone. Clinicopathologic analysis of thirty cases. The Journal of bone joint surgery American volume. 2006;88(9):1998–2008.

11. Gossai N, Hilgers MV, Polgreen LE, Greengard EG. Critical hypercalcemia following discontinuation of denosumab therapy for metastatic giant cell tumor of bone. Pediatric blood cancer. 2015;62(6):1078–80.

12. Matcuk GR Jr, Patel DB, Schein AJ, White EA, Menendez LR. Giant cell tumor: rapid recurrence after cessation of long-term denosumab therapy. Skeletal radiology. 2015;44(7):1027–31.

13. English WR, Lunt SJ, Fisher M, Lefley DV, Dhingra M, Lee YC, Bingham K, Hurrell JE, Lyons SK, Kanthou C, et al. Differential Expression of VEGFA Isoforms Regulates Metastasis and Response to Anti-VEGFA Therapy in Sarcoma. Cancer research. 2017;77(10):2633–46.

14. Zhang J, Dong J, Yang Z, Ma X, Zhang J, Li M, Chen Y, Ding Y, Li K, Zhang Z. Expression of ezrin, CD44, and VEGF in giant cell tumor of bone and its significance. World J Surg Oncol. 2015;13:168.

15. Shibuya M. Vascular endothelial growth factor and its receptor system: physiological functions in angiogenesis and pathological roles in various diseases. J BioChem. 2013;153(1):13–9.

16. Li J, Zhao X, Chen L, Guo H, Lv F, Jia K, Yv K, Wang F, Li C, Qian J, et al. Safety and pharmacokinetics of novel selective vascular endothelial growth factor receptor-2 inhibitor YN968D1 in patients with advanced malignancies. BMC Cancer. 2010;10:529.

17. Xie L, Guo W, Wang Y, Yan T, Ji T, Xu J. Apatinib for advanced sarcoma: results from multiple institutions' off-label use in China. BMC Cancer. 2018;18(1):396.

18. Zhu B, Li J, Xie Q, Diao L, Gai L, Yang W. Efficacy and safety of apatinib monotherapy in advanced bone and soft tissue sarcoma: An observational study. Cancer Biol Ther. 2018;19(3):198–204.
19. Wang Y, Min L, Zhou Y, Tang F, Luo Y, Zhang W, Duan H, Tu C. The efficacy and safety of apatinib in metastatic alveolar soft part sarcoma: a case series of six patients in one institution. Cancer management research. 2019;11:3583–91.

20. Wang G, Jiang S, Li Z, Dong Y. Denosumab and Sunitinib in the treatment of giant-cell tumor of bone with pulmonary and bone metastases in an adolescent: A case report. Medicine. 2019;98(46):e17778.

21. Li J, Zhou J, Liu Y, Sun X, Song W. Comprehensive treatment for multicentric giant cell tumors of the pelvis and spine using apatinib: A case report and literature review. J Cancer Res Ther. 2020;16(5):1020–6.

**Figures**

**Figure 1**

Radiological images of the proximal right tibia Radiograph (A, B) and CT (C, bone window), (D, soft-tissue window) showed osteolytic bony destruction. SPECT (E) were negative for metastatic lesions.
Figure 2

Radiological images of the proximal right tibia Radiograph (A, B), and CT (C, bone window) showed a circumferential lucency around the bone cement. MRI (D, T1-weight) showed a massive soft tissue mass.

Figure 3

Pathological features of the local lesions (A) High-magnification observation of numerous multinucleated giant cells (Hematoxylin and eosin stain, 200x). (B) High-magnification observation of local recurrence but without sarcomatous change (Hematoxylin and eosin stain, 200x). (C) Expression of VEGFR-2 in a tumor section (Immunohistochemical staining, 200x).
Figure 4

CT of the chest. (A) local recurrence but without pulmonary metastasis. (B) multiple pulmonary metastases were founded, denosumab initiated (C) 4 months after denosumab therapy (D) 3 months after denosumab and apatinib therapy (E) 15 months after denosumab and apatinib therapy (F) 33 months after denosumab and apatinib therapy