Heliyon 10 (2024) e36849

Contents lists available at ScienceDirect

Heliyon

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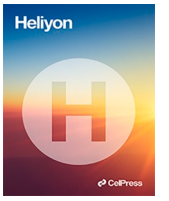

Case report

The successful control of multiple pulmonary metastasis from giant cell tumor of bone by monthly denosumab administration: A case report

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ARTICLE INFO

Keywords:
Giant cell tumor
Denosumab
Lung metastasis
Case report

ABSTRACT

Giant cell tumor of bone (GCTB) is a locally aggressive benign neoplasm that is associated with a large biological spectrum ranging from latent benign to highly recurrent and occasionally metastatic tumor. In this article, we present a case of a 37-year-old woman who presented with fracture at the distal femur due to GCTB. Bone segment resection and reconstruction were done, and histopathology showed tumor features for GCTB. Later, multiple lung metastasis was found 22 months post-operation, which was verified by biopsy. Then systemic denosumab therapy with different intervals (1-month and 2-month) was tried as the treatment. It was clarified that monthly denosumab administration, instead of 2-month interval, was required to control the progression of the unresectable multiple lung metastasis from GCTB, which could be a choice for the future treatment of these patients.

1. Introduction

Giant cell tumor of bone (GCTB) was first found by Cooper and Travers [1] in 1818. The tumor is generally benign and characterized histologically by multinucleated giant cells with a background of mononuclear stromal cells [2]. Despite being categorized as a benign lesion, GCTB could be locally aggressive and recur even after surgical resection [3]. Approximately 3 % of GCTB patients were found lung metastasis after tumor resection with a mean interval of 20 months [4–6]. The treatments for lung metastasis from GCTB usually consist of systemic therapies such as denosumab and interferons (IFNs), radiotherapy or even surgical resection [7,8]. However, there is no consensus on how to control it, especially for the unresectable multiple lung metastasis. In this paper, we aim to clarify the efficacy of denosumab administration with different interval (1-month and 2-month) for multiple lung metastasis from GCTB by presenting a detailed case.

2. Case presentation

A 37-year-old woman suffered a pathological fracture at the distal femur due to GCTB and was treated in our hospital by bone

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https://doi.org/10.1016/j.heliyon.2024.e36849
Received 28 April 2024; Received in revised form 11 June 2024; Accepted 22 August 2024
Available online 25 August 2024

segment resection and reconstruction. In Fig. 1A and B, the pre-operative CT images (transverse and lateral views) showed that the cortical bone of the distal femur were disrupted indicating a fracture and an obvious trabacular bone loss was seen in the lesion. The MRI images indicated that there were giant cell tumor of bone-like changes and surrounding bone marrow edema in the lesion (Fig. 1C and D). To verify its diagnosis, the biopsy indicated by Fig. 1E was taken for histology and it was confirmed that osteoclastic giant cells with a variable number of nuclei were seen among the un-organized tumor cells. No osteoid, necrosis and hemorrhage were seen among the lesion, indicating the primary lesion is not malignant (Fig. 1F).

In view of tumor involving knee joint and leading pathological fracture (Campanacci III), bone segment resection and joint replacement were done. The resected tumor tissue were shown in Fig. 2A and B, the fracture line was also seen across the articular surfaces. After reconstruction, the joint prosthesis was in good position to keep the function of the knee (Fig. 2C and D). The post-operative CT of the lung showed no sign of metastasis (Fig. 2E).

After the surgery, this patient was under regularly inspection. The multiple lung metastasis was found from CT of the lung at a follow-up of 22-month post-operation (Fig. 3A). Then CT-guided biopsy was done from one of the nodules in the lung (Fig. 3B). The histology showed that there were giant tumor cells with multiple nuclei in the normal lung tissue (Fig. 3C). Since the multiple lung metastasis was seen in various location and thus unresectable, it was treated by denosumab administration with different intervals. She was also placed on daily calcium and vitamin D supplements. The whole treatment timeline and follow-up was shown in Fig. 4.

During the treatment for multiple lung metastasis, it was found that monthly administration of denosumab could effectively hinder the progression of the metastasis and even decrease the size of the tumor (Fig. 5A and B). After changing the treatment protocol to 2-month interval, the size of the tumor obviously increased, especially in the upper part of the lung (Fig. 5B and C). As a result, we had to revise the denosumab administration back to 1-month interval. Interestingly, the lung nodules decreased again by their sizes (Fig. 5C and D). The size of each lung nodule was described in Table S1.

3. Discussion

In this paper, we found that monthly denosumab administration, instead of 2-month interval, is effective and required to control the progression of multiple lung metastasis from GCTB. Furthermore, regular chest CT scan is needed to monitor the development of lung metastasis from GCTB.

As we know, GCTB is usually considered to be locally aggressive, with a tendency for local recurrence with occasional metastatic potential [9]. Generally, the rate of lung metastasis from GCTB is very low. It has been reported that the lung metastasis rate among these cases is between 2.1 and 4% [10–13]. Several risk factors have been found be associated with the lung metastasis. Kay et al. [14] suggested that the surgical method was a risk factor and described that the patients who underwent resection of the primary lesion instead of curettage had a lower metastasis rate. Niu et al. also found that the local recurrence rate in the resection group (1.6 %) was significantly lower than that in the curettage group (8.6 %) [13]. Yang et al. showed that local recurrence, a high Campanacci stage, and curettage were possible high-risk factors for pulmonary metastasis [15]. In our case, we did wide resection for the GCTB and no

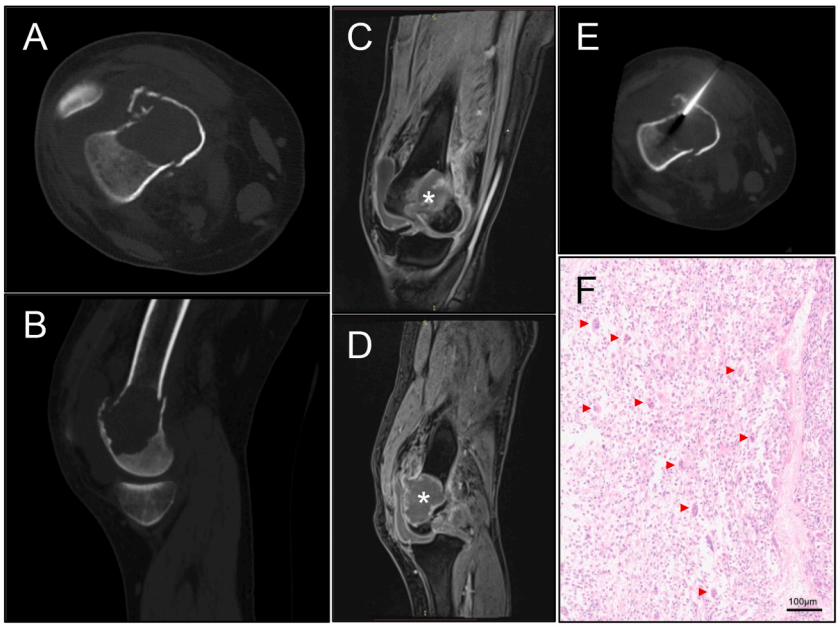

Fig. 1. The pre-operative evaluation of the patient with fracture in the distal femur due to GCTB. A-B indicated the fracture in the distal femur due to GCTB by CT. C-D showed the condition of tumor in the bone, * indicates the GCTB lesion. E showed that the location of CT-guided biopsy was taken in the center of the tumor. F showed the histology of the tumor tissue, the red arrow indicates the osteoclastic giant cells with multiple nuclei.

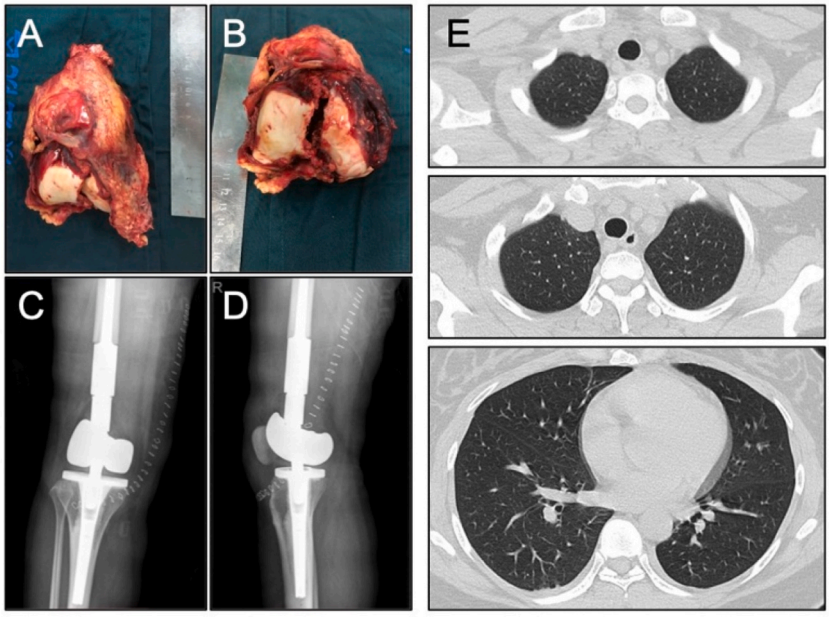

Fig. 2. The post-operative inspection of the patient in the surgical site and lung. A-B showed the overview of the resected tumor tissue and distal femur. C-D showed that the joint prosthesis was placed in the resected area by X-ray. E showed no metastasis was seen in the lung by CT.

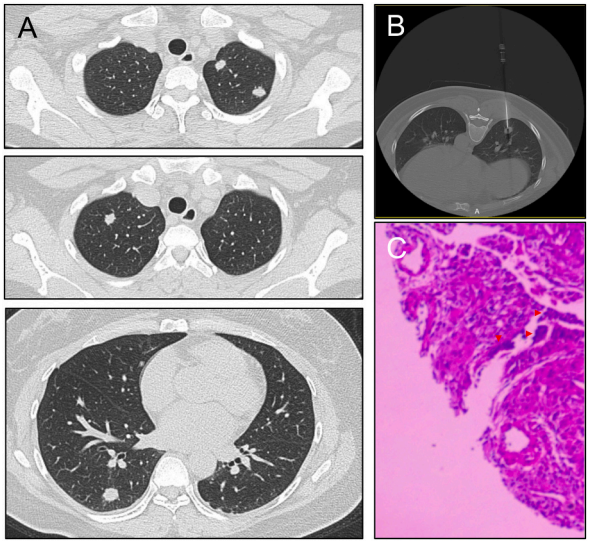

Fig. 3. The discovery of multiple lung metastasis from GCTB and its verification by CT-guided biopsy. A showed that in total 4 nodules were found from CT scans at different locations. B showed that CT-guided biopsy was taken from one of the nodules. C showed that giant tumor cells with multiple nuclei sitting in the normal lung tissue, immunochemistry staining (IHC): TTF-1 epithelium (+) , CK(AE1/AE3) epithelium (+) , EMA (+) , S-100 (−) , SMA (−) , Desmin (−) , CD34 (−) , Ki-67 5 % (+) , Bcl-2 (−) , TLE1 giant cell (+) , ALK giant cell (+).

local recurrence was found during the whole follow-up, which indicates that the initial fracture due to GCTB might be a risk factor for the post-operative lung metastasis. Previous study has shown that circulating tumor cells (CTCs) could impact metastasis formation [16]. However, whether it is the reason for the multiple lung metastasis even after wide tumor resection is still not clear. Thus, more basic and clinical studies need to be done for further validation. Another risk factor is the location of the GCTB as reported before [17]. The GCTB in the distal femur, especially Campanacci III, has higher risk of post-operation lung metastasis [18]. More attention needs to be paid for its perioperative treatment. Our study has also clarified the importance of regular follow-up, especially the chest CT scan. It has been reported that average interval from surgery of primary tumor to detection of pulmonary metastasis was 15 months [19]. Other study indicated that the development of lung metastasis from GCTB without local recurrence could even happen 43 months after surgery [15]. Thus, regular chest CT scan is still recommended during the post-operation follow-up.

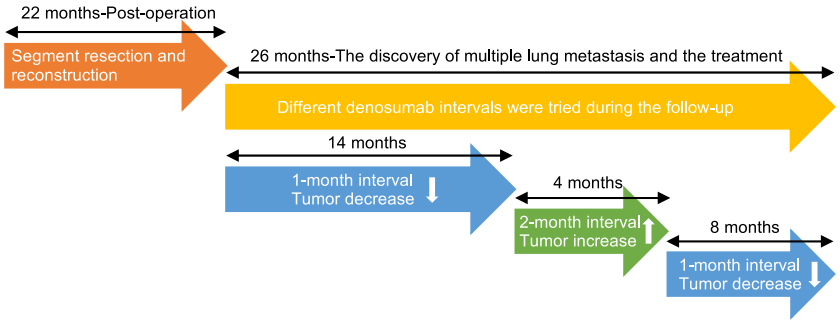

Fig. 4. The timeline of post-operative follow-up and treatment protocols for multiple lung metastasis.

After being diagnosed by CT scans, the lung metastasis is usually treated by metastasectomy [20] or chemotherapy like denosumab [21], interferon-α [22], bisphosphonates [23] and so on. But treatment recommendations for lung metastases vary and no consensus has been reached especially for multiple lung metastasis. In this study, we found 4 nodules in different location of the lung, which was not suitable for metastasectomy. Denosumab, a human monoclonal antibody directed against the RANKL, has been found effective to control the progression of GCTB by suppressing the recruitment of osteoclast-like giant cells and avoiding the osteolysis [24,25]. It has also been found effective for metastatic GCTB [24]. A few studies described the denosumab administration for metastatic GCTB (Table S2). Two studies have tried 120 mg loading for first 3 weeks followed by every month and found its efficacy of controlling lung metastasis from GCTB [26,27]. Demirsoy U et al. [28] found the early rapid response to denosumab (2 course) in metastatic GCTB within only 2-month follow-up. However, few studies have explored the optimized dose for multiple lung metastasis from GCTB [29]. In our study, we found that monthly administration of denosumab could effectively hinder the progression of the multiple lung metastasis and even decrease the size of these lesions. And the first 3 loading doses within a month as reported before were not required. No loading doses of denosumab was reported for GCTB before [28]. However, its long-term effect is still unclear. Thus, we have applied this regimen in this case and finally confirmed its efficacy. Considering the dose-dependent increase in side effects of long-term denosumab administration, such as osteonecrosis of jaw, mild peripheral neuropathy or atypical fracture [30], we extended interval to 2 months. However, denosumab administration with 2-month interval showed no efficacy and even these lesions had increased by short period. Thus, we do suggest that 1-month interval is required for using denosumab to control the multiple lung metastasis from GCTB, which could be included in the guideline for the treatment of these cases. More studies need to be done to validate its efficacy in the future.

As reported, denosumab is usually a well-tolerated drug. Most common side effects are hypocalcemia, hypophosphatemia, increased bone mineral density, risk for fracture, and osteonecrosis (31). In our patient, because of decreased bone turnover during denosumab treatment, we used prophylactic vitamin D and calcium supplementation. The patient has had no hypocalcemia or hypophosphatemia, but we still need to look for long-term complications.

4. Conclusion

GCTB is normally considered a benign bone tumor. However, it may occasionally metastasize to the lung with multiple lesions, which should be monitored by regularly post-operative CT scans. Monthly denosumab administration, instead of 2-month interval, is required to control the progression of multiple lung metastasis, which could guide the treatment for these cases in the future.

The ethics

This study was performed in accordance with the provisions of the Declaration of Helsinki and the International Conference on Harmonization guidelines for Good Clinical Practice, and was approved by the institutional review boards of The Second Affiliated Hospital of Zhejiang University School of Medicine (SAHZU) with the institution review board (IRB) approval number I2024442. This patient provided signed written informed consent before enrollment.

CRediT authorship contribution statement

Yang Liu: Writing – original draft, Data curation. **Meng Liu:** Writing – review & editing, Conceptualization. **Zhaoming Ye:** Writing – review & editing, Conceptualization. **Hengyuan Li:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

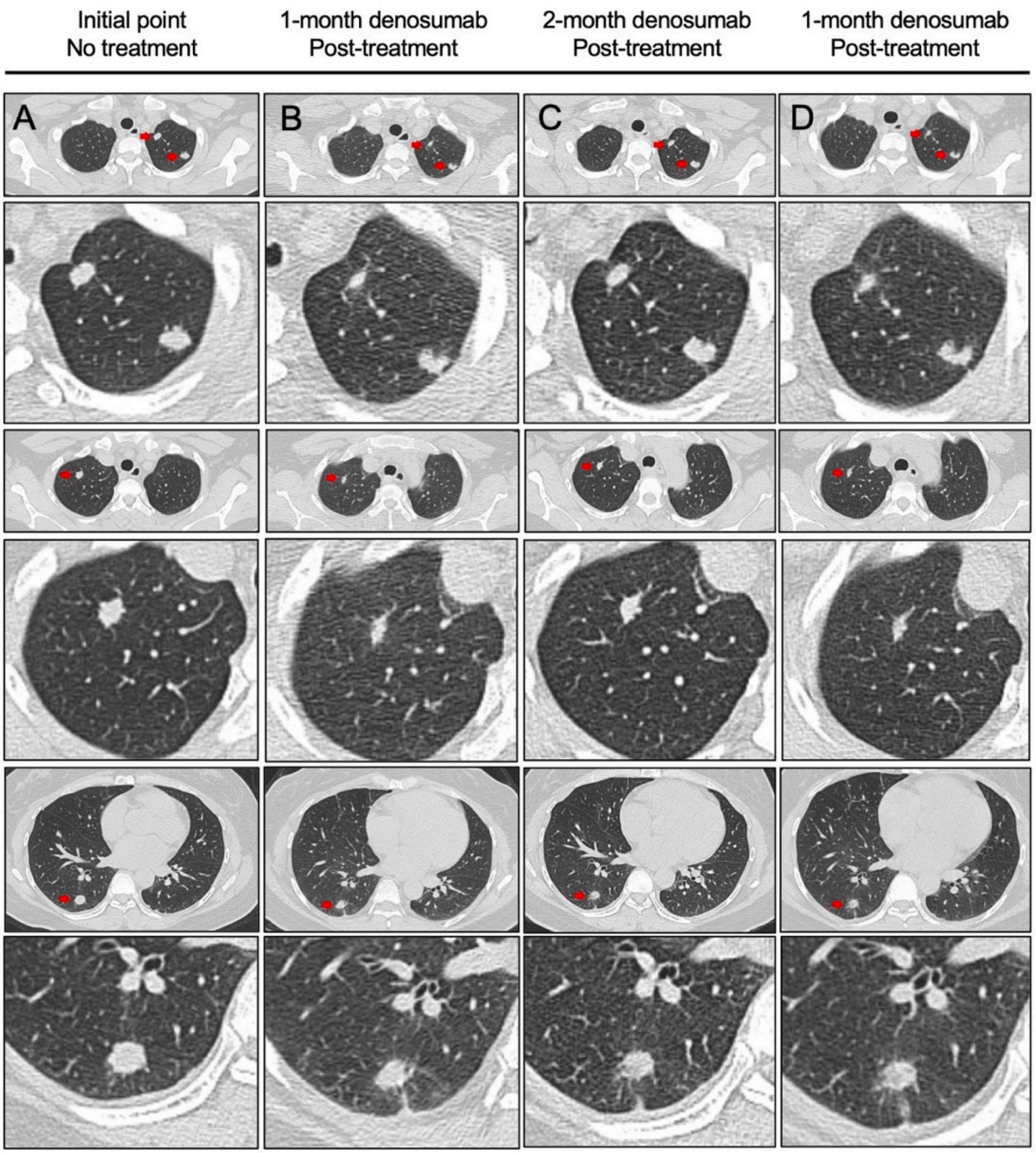

Fig. 5. The CT scans to evaluate the multiple lung metastasis during the follow-up. A showed the initial time point when the multiple lung metastasis was found. B showed that the size of the lung nodules decreased after being treated by monthly denosumab administration for 14 months. C showed that the size of lung nodules increased after being treated by denosumab administration with 2-month interval for 4 months. D showed that the size of the lung nodules decreased again after changing the treatment protocol back. The red arrow indicates the location of multiple lung metastasis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e36849.

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