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# Bisphosphonate treatment as a safe choice for treating lung metastases of recurrent giant cell tumor of bone

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## ABSTRACT

Giant cell tumor (GCT) accounts for 5% of all primary bone tumors and 20% of benign skeletal tumors. This case report presents the case of a 17-year-old female with a recurrent giant cell tumor and lung metastases. The patient received bisphosphonate therapy instead of surgery. The use of zoledronic acid for lung metastases from GCT may have conservatively improved clinical symptoms and radiological assessments can be achieved.

**Key words:** bisphosphonate, giant cell tumor, recurrence

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## Introduction

Giant cell tumor (GCT) accounts for 5% of all primary bone tumors and 20% of benign skeletal tumors. It is common in young adults aged between 20 and 40 years, with a slightly higher incidence in females. GCT metastases to the lung, lymph nodes, liver, soft tissues, brain, mediastinum, scalp, or kidney are fairly rare. The recurrence rate is only about 3%. Inappropriate surgical treatment may lead to increased osteolysis and destruction of the joints adjacent to the primary site. The currently available treatment options for these metastases are metastasectomy, chemotherapy, denosumab, interferon, or bisphosphonates [1, 2]

In this case report, we aimed to evaluate outcomes for a GCT patient with metastases to the lung, who received long-term oral bisphosphonate. The purpose of this study is to show that bisphosphonate is a safe and viable option to achieve good outcomes.

## Case presentation

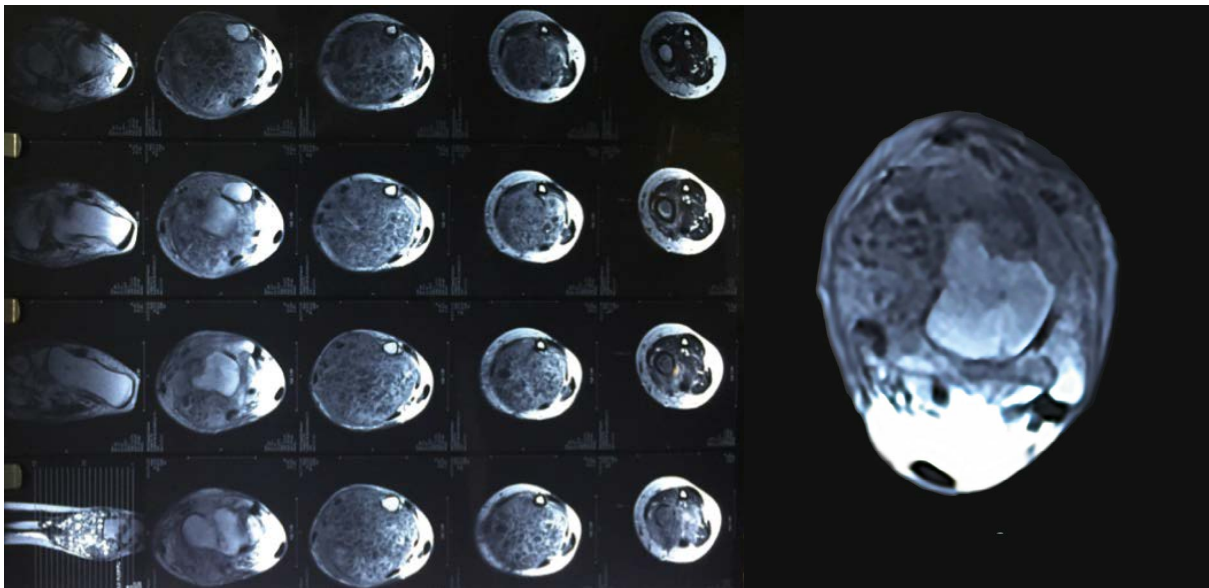
A 17-year-old female presented to the Orthopaedic Clinic of Sanglah General Hospital Denpasar Bali. The patient reported a painful lump on her ankle that she had first noticed 8 months earlier. This issue started with a small lump on the left ankle which gradually grew. At the same time, the pain gradually worsened especially in the preceding 5 months (Fig. 1). At the same time, she suffered from weight loss. She presented with swelling, local tenderness, and a 6 x 6 cm mass with an irregular margin at her distal left tibia. Radiological investigation using plain X-ray and magnetic resonance imaging (MRI) of the ankle was then performed, revealing lytic lesion and cortical destruction on the epiphysis of the distal tibia (Fig. 1, 2) without any metastases to the lung (Fig. 3) — suggesting Enneking stage 3 or Campanacci grade III giant cell tumor of the distal tibia.

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**Figure 1.** Clinical picture and radiography examination of the left ankle



**Figure 2.** Magnetic resonance imaging of the ankle showed cortical destruction of the distal left tibia with minimum soft tissue involvement

The patient was then admitted for inpatient care and first underwent an open biopsy and frozen section. The histopathology analysis found dense proliferation of spindle mononuclear cells, which confirmed the suspicion of GCT. After this diagnosis, we performed extensive resection followed by fibula and ankle arthrodesis tibial reading as a curative treatment for the lesion (Fig. 4). The post-operative X-ray is shown in Figure 5. The patient also underwent bisphosphonate treatment for 18 months after the resection procedure to prevent any local recurrence and metastases.

Two years after the surgery, the patient returned to the hospital with a new complaint of shortness of breath

aggravated by activity and slightly reduced after rest. A chest X-ray and computed tomography (CT) scan were performed to assess whether any lung metastases had occurred. The chest X-ray showed coin lesions with suspected embolism or metastasis while the CT-scan of the chest revealed multiple enhanced solid nodules in the perihilar segment of the lung. An X-ray of the left ankle also showed lytic lesions at the distal region indicating recurrence (Fig. 6). Cardiothoracic surgeons were consulted for any possible metastasectomy procedure, but there was a considerable risk. Therefore, the patient opted for conservative treatment for the lung metastases, with further 5 months of bisphosphonate

therapy. For the primary tumor, the patient underwent a curettage procedure with highspeed burr and phenol followed by bone cement filling to repair the defect (Fig. 6, 7). She then received 4 mg of zoledronic acid in 6 cycles and was able to walk pain-free with no crutches after 6 months.

The patient underwent bisphosphonate therapy that consisted of a monthly dose of 4 mg zoledronic acid for 6 consecutive months following the metastasis discovery.

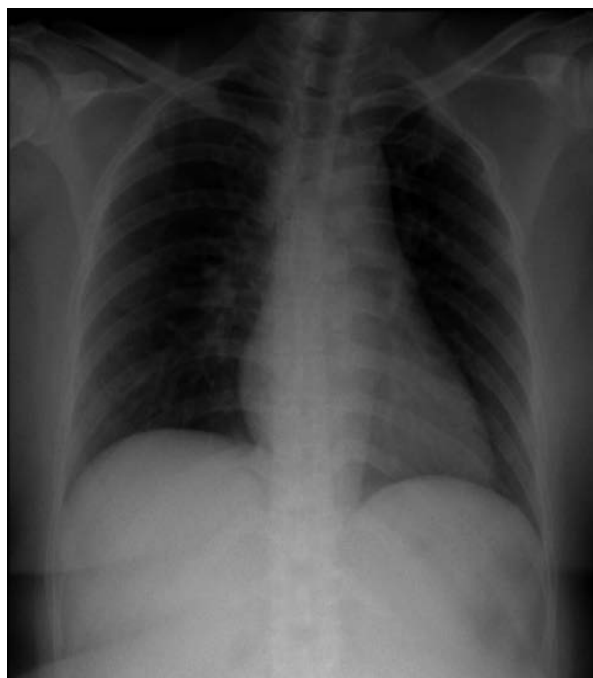


Figure 3. Chest X-ray

Five months follow-up after initiation of bisphosphonate therapy showed a favorable outcome based on clinical and radiological evaluations. The patient had no complaints about shortness of breath and has been able to do daily activities without any difficulty. A chest X-ray and CT scan showed significant differences after zoledronic acid therapy (Fig. 8, 9).

## Discussion

Local recurrence of GCT is rather common, ranging from 10 to 26.9%, with extra-compartmental (soft tissue) extension and tumor grade considered the most significant risk factors [3]. With regards to metastases, the lungs are the most common site where GCT metastases frequently occur. Its incidence is estimated to be as much as 5% of bone GCT, especially in younger patients with grade 3 Enneking disease [4–6].

In this case, a CT scan identified pulmonary emboli which were visible as multiple enhanced solid nodules in almost all segments of the lung. This patient was placed under the joint care of thoracic and vascular surgeons. Following discussions with the patient, we decided to treat the metastases with conservative treatment instead of a surgical procedure. Follow-up conducted 5 months after the initiation of conservative bisphosphonate zoledronic acid therapy found significant improvement of the lung lesions. This is in line with previous findings by Zekri et al. [7], which showed that zoledronic acid's antitumor effect is mediated through inhibition of tumor cells proliferation, induction of apoptosis, synergistic/additive to the inhibitory effect of cytotoxic agents,

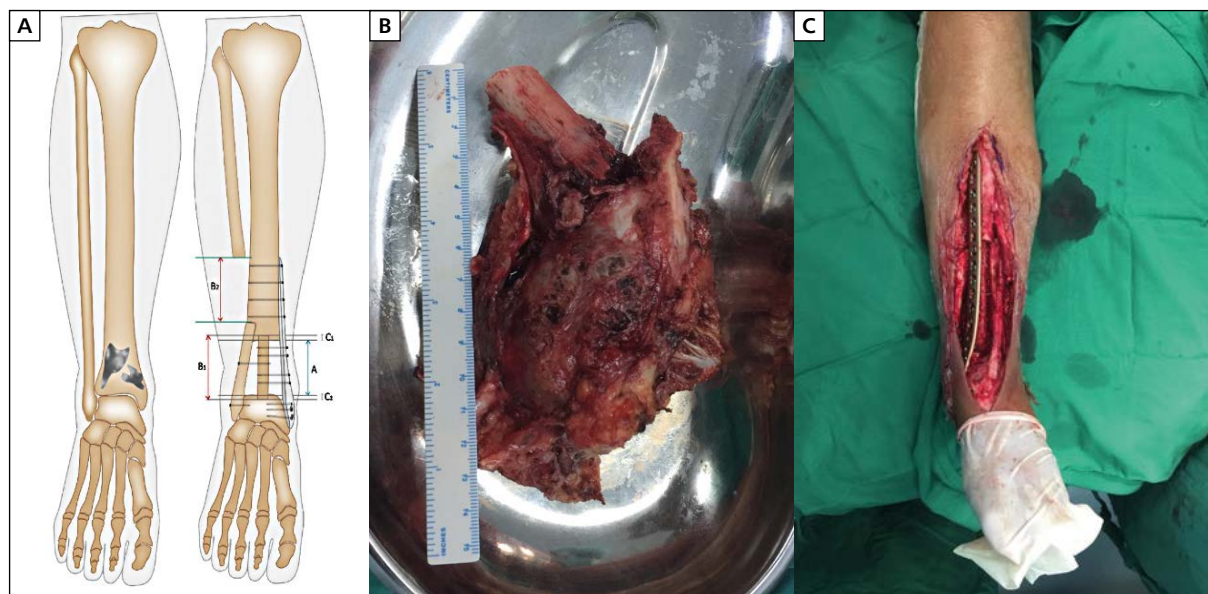


Figure 4. Clinical picture of the surgery showing; A. Pre-operative planning; B. The resected tumor with a 2 cm margin of healthy soft tissue; C. Clinical condition after fixation with autologous strut graft from the fibula



inhibition of angiogenesis, decrease of tumor cells adhesion to the bone, decrease of tumor cells invasion and migration, disorganization of cell cytoskeleton and activation of a specific cellular antitumor immune response.

Bisphosphonates are stable analogs of inorganic pyrophosphate in which the oxygen atom of the P-O-P bond is replaced with a non-hydrolyzable P-C-P bond. Bisphosphonates inhibit osteoclast activity by several mechanisms which depend largely on their chemical structure. Bisphosphonates have been shown to induce apoptosis of tumor cells and inhibit tumor cell growth of a variety of tumor cell types [8].



Figure 5. Post-operative X-ray

Zoledronic acid has a high affinity for mineralized bone accumulating rapidly after intravenous administration and localizing preferentially at sites of high bone turnover. It is thought to be internalized during bone resorption via the endocytic activity of osteoclasts and inhibits bone resorption by inhibiting farnesyl pyrophosphate synthase (FPPS) and preventing protein prenylation. The binding affinity of zoledronic acid for hydroxyapatite was higher than that of other bisphosphonates (binding affinity constants of  $3.47 \times 10^{-6}$  mol/L vs. 2.94, 2.36, 2.19, 1.19 and  $0.72 \times 10^{-6}$  mol/L for alendronic acid, ibandronic acid, risedronic acid, etidronic acid, and clodronic acid, respectively) [9]. Zoledronic acid has also been considered a reasonable, effective treatment for unresectable lesions [7, 10].

Unlike bisphosphonate, the optimal duration, long-term safety, maintenance dose, and optimum indications of denosumab in GCT treatment remain to be elucidated. A recent in-depth review by Li et al. [11] warns that denosumab therapy of GCT of the bone (GCTB) should be applied with caution. Furthermore, denosumab is also still associated with a probable increase of local recurrence in patients treated with curettage [11].

In this study, we conducted bisphosphonate therapy using zoledronic acid in a patient who had lung emboli due to metastases of GCT. Bisphosphonate has shown a promising result in treating metastases of GCT. The anti-osteoclast effect of bisphosphonates and their ability to prevent bone resorption make bisphosphonates a potential treatment for GCT, and several studies have confirmed its efficacy [10]. However, in this study the patient had a recurring case of GCT in the left ankle based on clinical symptoms and radiographic examination. The study conducted by Xu et al. [12] showed that the recurrence rate of GCT was 2.1%, and the mean interval time was  $11.3 \pm 4.1$  months with a range from 5–17 months.

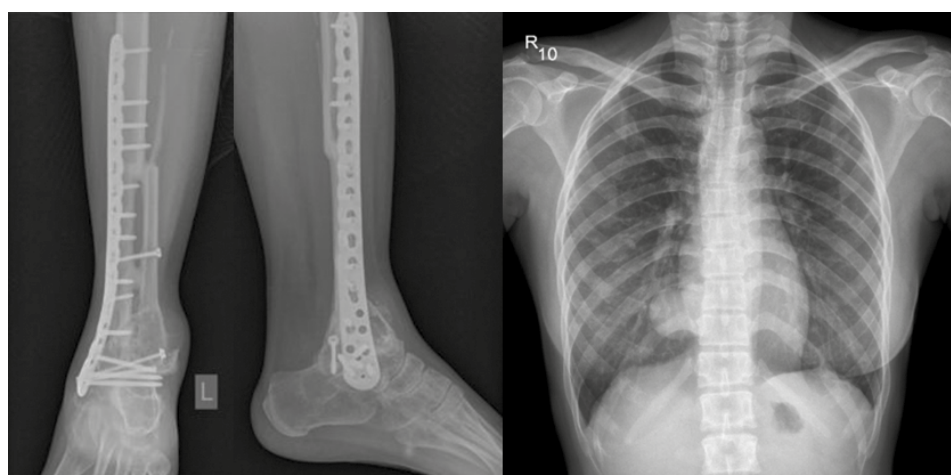


Figure 6. Chest and ankle X-rays taken 2 years after the first surgery, showing recurrence at the initial primary site with metastases to the lung despite receiving 6 months of bisphosphonate treatment

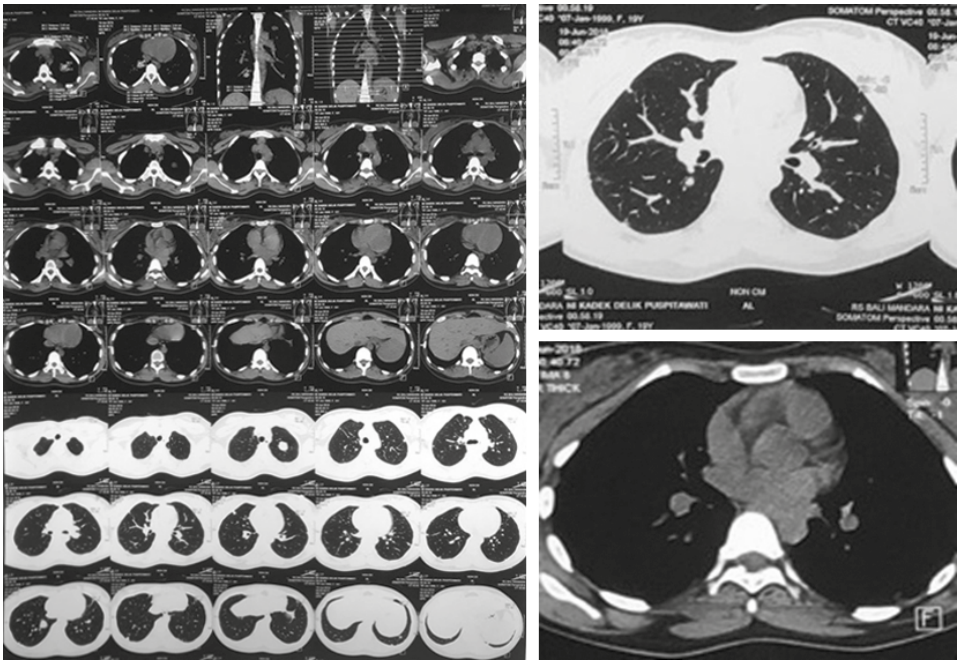


Figure 7. Chest computed tomography scan after 2 years after surgery, showing metastatic nodules at almost all lobes of the lung

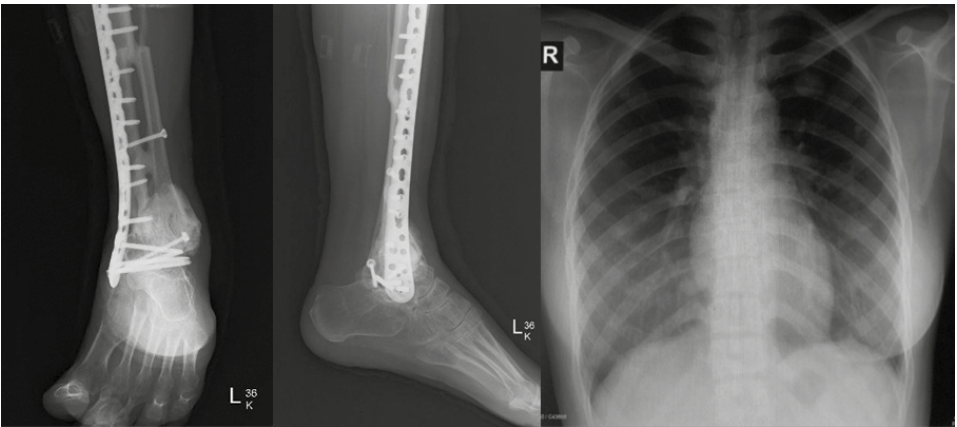


Figure 8. Chest and ankle X-Ray post-surgical bone graft and bisphosphonate therapy

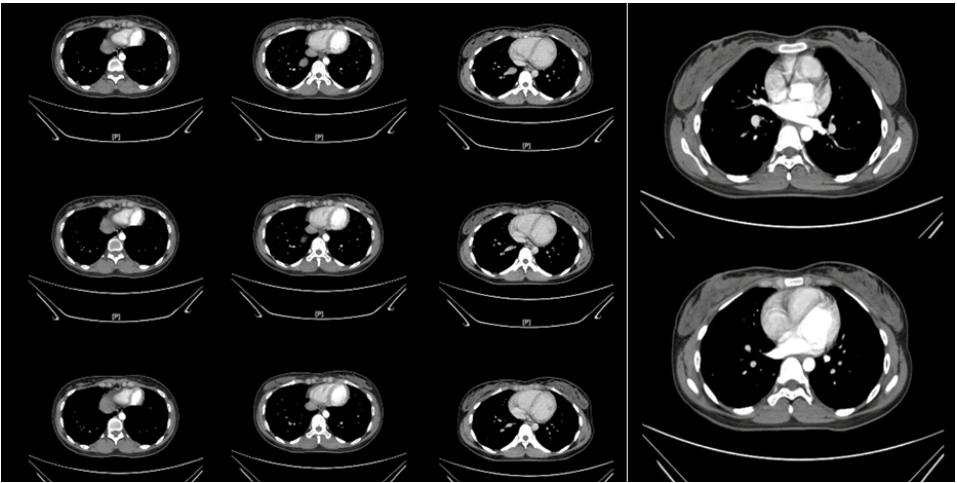


Figure 9. Chest CT scan after bisphosphonate therapy

In a previous study reported by Balke et al. [13], the authors examined clinical and radiological outcomes of bisphosphonate treatment in 25 cases of aggressive primary, recurrent, and metastatic giant cell tumors from 4 European centers. They reported no signs of progression or increase in the size or number of lung metastases in GCT patients who were treated with bisphosphonates. The use of bisphosphonate to treat pulmonary metastases in GCT has also been reported by Dubey et al. in 2019 [14]. They reported that the usage of bisphosphonates successfully reduced chest pain and controlled tumor growth, as soon as 3 months after therapy.

In our case, bisphosphonate therapy has been successful in controlling the lung metastases of the GCT. Even though this finding is based only on observation, we argue that it is still a viable safe first-line method of managing patients with lung metastases from GCBT [14, 15]. We propose that surgical metastasectomy could be delayed for such metastases and reserved for cases that are resistant to bisphosphonate therapy.

## Conclusion

Improvement in clinical symptoms and control of tumoral growth in the case of lung metastases of GCT could be achieved conservatively by using zoledronic acid.

## Consent

Written informed consent was obtained from the patient for being included in the study and its publication.

## Ethics statement

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

## Author contributions

N.H.K.: study concept and design, performed surgery, final editing and publication; K.P.B.S.: data collection and drafting; W.I.G.E.: performed surgery.

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## Conflict of interest

Authors declare no conflict of interest.

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