Giant Cell Tumors of the Bone With Pulmonary Metastasis

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**abstract**

Giant cell tumors of the bone are benign but locally aggressive, and they rarely metastasize to the lungs. The purpose of this study was to retrospectively review the clinical presentation, long-term outcomes, and treatment of pulmonary metastasis of these tumors. Between 1991 and 2004, a total of 168 patients with giant cell tumors of the bone were treated at the authors’ institution, 7 of whom developed lung metastasis. Four of the 7 patients were men, and mean age of these patients at initial surgery was 40 years (range, 19-56 years). All patients underwent wide excision and reconstruction or curettage and bone grafting for the bony lesions. Lung metastases were detected at a mean of 44 months after the treatment of bone lesions. Five patients had multiple metastases, and 2 had solitary pulmonary metastases. Six of these patients underwent delayed treatment, locally aggressive, or multiple recurrent and surgical procedures. All of the aforementioned procedures had similar risk factors to those previously reported in the literature. One patient had multiple giant cell tumors of the bone. At last follow-up, 2 patients had died due to complications from the pulmonary metastases or chemotherapy. One patient underwent a metastasectomy 4 years after treatment due to the progression of pulmonary metastasis. The remaining 4 patients were alive and healthy after chemotherapy or conservative treatment. Therefore, early detection, adequate treatment of the primary bone lesion, conservative treatment of lung metastases, and regular long-term follow-up are recommended. [Orthopedics. 2016; 39(1):e68-e73.]

A giant cell tumor (GCT) of the bone is a benign but locally aggressive bone tumor. Giant cell tumors of the bone are found predominantly in the epiphysis and metaphysis of long bones in young adults. Enneking described a staging system for benign bone tumors that is commonly used for classifying GCTs of the bone. According to this system, there are 3 stages: stage 1, latent; stage 2, active; and stage 3, aggressive. Metastasis of GCTs of the bone is extremely rare. Finch and Gleave first reported lung metastasis of a benign GCT of the bone in 1926, and since then, other such case reports and series have been published. Metastasis of GCTs of the bone occurs in the lymph nodes, bone, muscle, skin, and breast, but it most commonly arises in the lungs, in which the incidence ranges from 1% to 9%. Pulmonary metastases usually have the same histological features as the benign primary tumor. There are several etiologies and mechanisms for the metastasis of GCTs of the bone, including transformation from a self-limited benign course and true arterial metastasis.

The treatment of pulmonary metastases of GCTs of the bone includes observation,
The purpose of this retrospective study was to review the clinical presentation, long-term outcomes, and treatment of patients with pulmonary metastasis from GCTs of the bone.

**Materials and Methods**

This retrospective study was approved by the institutional review board at the authors’ institution (No. 103-4341B). The authors retrospectively retrieved data from their institution’s medical records and found 168 patients who were treated for primary GCTs of the bone or referred from other hospitals due to recurrence between 1991 and 2004. Chest radiography had been performed routinely in these patients before the bone lesion was treated. Seven (4%) of the 168 patients were identified as having pulmonary metastasis of GCTs of the bone. The remaining 161 patients were not diagnosed with pulmonary metastatic disease during the initial intervention and follow-up. Treatment of the primary lesion included curettage and bone grafting or wide excision and reconstruction. For pulmonary metastasis, observation, surgical resection combined with chemotherapy (using doxorubicin and ifosfamide), or chemotherapy (doxorubicin and ifosfamide) alone were performed.

Five patients were followed up annually, and radiographs of the primary lesion site and chest were taken to evaluate the local condition and pulmonary metastases. The remaining 2 patients died of complications from metastatic lung disease 6 months and 2 years after treatment of the bone lesion at the authors’ institution, respectively.

All clinical features of the 7 patients, including age, gender, radiological findings, primary surgical details, pathological results, follow-up details (such as the occurrence of local recurrence and metastasis), and therapeutic management of metastasis, were obtained from the medical records during a mean of 110 months (range, 6-235 months) of follow-up after the first operation at the authors’ this institution. Demographic data for all patients are presented in the Table.

**Results**

Seven patients (3 women and 4 men) with a mean age of 40 years (range, 19-56 years) at diagnosis developed pulmonary metastasis at a mean of 44 months (range, 9-132 months) after treatment for bone lesions.

The localization of the primary tumors was the proximal humerus (n=1; case 7), distal humerus (n=1; case 6), proximal femur (n=1; case 2), distal femur (n=2; cases 3 and 4), and proximal tibia (n=2; cases 1 and 5). The primary tumor was predominantly located around the knee joint in 4 patients (57%).

One of the patients (case 3) had a stage 2 lesion according to the Enneking clas-
sification and was treated with curettage
and morselized bone graft for the primary
tumor. Due to recurrent or delayed treat-
ment and large stage 3 tumors, the other 6
patients were treated using wide resection
and arthrodesis (n=1; case 1), wide resec-
tion and endoprosthesis replacement (n=3;
cases 2, 4, and 7), or wide resection plus
reconstruction with structural allogeneic
bone graft (n=2; cases 5 and 6).

Five of the patients (cases 1, 2, 4, 5,
and 7) were transferred from other hos-
pitals due to recurrent GCTs of the bone.
One patient (case 3) who was initially
treated at this institution had repeated
recurrences of GCTs during follow-up.
She underwent 5 curettage or excision
procedures for the bone or soft tissue
recurrences. One patient (case 6) un-
derwent excision of the GCT of the left
scapula at another hospital 2 years before
admission for a GCT of the right humeral
condyle.

Pulmonary metastasis was diagnosed
at a mean of 44 months (range, 9-132
months) after the initial operation for
bone lesions. Five (71%) patients were
diagnosed with lung metastasis within
3 years (range, 9-34 months) postopera-
tively for bone lesions. One patient (case
7) was diagnosed with pulmonary metastasis
approximately 10 years later due to
delayed treatment. Solitary metastases
were noted in 2 patients (case 3 and 4),
whereas 5 patients had multiple meta-
static lesions.

The treatment for metastasis was ob-
servation in 4 patients (cases 2, 3, 4, and
6), and 1 of these patients (case 4) un-
derwent lobectomy due to metastatic pro-
gression after 4 years of follow-up. Two
patients received chemotherapy (cases 1
and 7), whereas a combination of surgical
resection and chemotherapy was per-
formed in 1 patient (case 5).

Three of the patients who received
conservative treatment for pulmonary me-
tastasis had no further progression during
follow-up. For 1 of the 3 patients (case 2),
pulmonary metastases spontaneously re-
gressed within 1 year after curative treat-
ment of her bone lesion. Growth cessation
of pulmonary metastasis occurred in the
other 2 patients (Figure 1). Lastly, the pa-
tient (case 1) who received chemotherapy
was healthy after 18 years of follow-up,
with no local recurrence of the bone lesion
and regression of pulmonary metastasis
after chemotherapy (Figure 2).

Two (29%) of the 7 patients died dur-
ing treatment. One patient (case 7) died
due to complications of chemotherapy
(bone marrow suppression, followed by
sepsis and respiratory failure), and the
other patient (case 5) died due to respira-
tory failure caused by uncontrolled met-
astatic disease even after metastasectomy
and chemotherapy. The overall prognosis
and survival rate for pulmonary metastasis
were favorable.

**Figure 1:** Case 3. Posteroanterior chest radiograph of a 29-year-old woman who had solitary pulmonary metastasis (arrow) (A). Posteroanterior chest radiograph taken after the bone lesion was successfully cured showing the progressive growth of the metastatic lesion (arrow) ceased (B).

**Figure 2:** Case 1. Posteroanterior chest radiograph of a 21-year-old man who had multiple pulmonary metastases (A). Posteroanterior chest radiograph taken after chemotherapy showing that the metastases had regressed; the patient has remained healthy during follow-up (B).
Discussion

Giant cell tumors of the bone are benign but locally aggressive tumors. Metastasis occurs rarely, and it most commonly develops in the lungs. Both pulmonary metastases and primary lesions are histologically benign.\(^2\) Pulmonary metastases can be solitary or multiple. In this study, 5 (71%) patients had multiple pulmonary metastases.

Pulmonary metastatic lesions can be classified according to their growth patterns as follows: (1) those with spontaneous regression or growth cessation; (2) those with continuous slow growth; and (3) those with rapid growth.\(^9\) In the current study, after curative treatment of the bone lesion(s), pulmonary metastases spontaneously regressed within 1 year in 1 patient and growth of the lesions ceased in 2 patients. In 1 patient, pulmonary metastasis was silent initially after treatment, but it progressed 4 years later. This may indicate that regular follow-ups for pulmonary metastasis are important even in initially dormant tumors.

The incidence of pulmonary metastasis (4%) in the current series is similar to that reported in previous literature (1% to 9%).\(^3,11\) The interval between the diagnosis of the primary tumor and the pulmonary metastases ranged from 9 to 132 months (mean, 44 months) in the current study, which is also in agreement with the reported literature,\(^7,16\) wherein most metastases occurred within the first few years. Tubbs et al\(^11\) reported that 54% of patients experience pulmonary metastasis within 3 years and 92% develop metastasis within 7.5 years. However, Siebenrock et al\(^10\) reported a maximum time of 24 years in the development of metastasis in 1 patient.

According to a report by Rock et al,\(^14\) the predominant primary site for metastatic GCTs is the distal radius. However, in the current series, no primary tumors were located on the distal radius. Four (57%) patients had primary tumors around the knee joint (proximal tibia and distal femur). Dominkus et al\(^13\) also found that the primary tumor was predominantly located around the knee joint (71%). Other studies have also revealed that most GCTs arise around the knee joint.\(^5,15,16\) This may explain why most patients with pulmonary metastasis have primary tumors around the knee joint.

Other risk factors for pulmonary metastasis include locally aggressive tumors and multiple recurrences.\(^7,8,10,13\) Six patients in the current study had Enneking stage 3 lesions. Six patients had local recurrences before or after pulmonary metastasis was detected. All cases of pulmonary metastasis in the current series were locally aggressive.

Three patients had large tumors with large soft tissue masses (Figure 3), and all received delayed intervention for the primary or recurrent tumors. This indicates that delayed treatment of the primary or recurrent tumors may increase the risk of pulmonary metastasis. One patient in this series had multiple GCTs of the bone. Because of the small number of cases and few reports of multiple GCTs of the bone, the relationship between multiple GCTs of the bone and pulmonary metastasis remains unclear.

According to a report by Viswanathan et al,\(^7\) there is no association between metastasis and risk factors, such as locally aggressive disease, multiple recurrences, and the distal radius as the primary site. Reports suggested that surgical manipulation promotes pulmonary metastasis;\(^17\) thus, the number of operative procedures to control primary lesions may be a factor in the development of lung metastasis.\(^10\) One patient (case 3) in this series had repeated recurrent tumors and underwent excision for the recurrent tumors 5 times. Solitary pulmonary metastasis was noted during the period of repeated operation, but the metastatic disease was dormant after the local recurrences were controlled.

Recently, some studies provided biomarkers that predicted the aggressive behavior of GCTs of the bone. Gambri et al\(^18\) reported that the level of expression and incidence of overexpression of factors including interleukin-6, as well as urokinase-type plasminogen activator and its inhibitor PAI-1, were higher in primary GCTs of the bone that relapsed and metastasized to the lungs. The evaluation of the expression levels of these proteins at the time of diagnosis may predict the aggressive behavior of GCTs of the bone.\(^19\) Horvai et al\(^19\) reported that human telomerase reverse transcriptase was correlated with recurrence-free survival (\(P=.02\), and metastasis-free sur-
vival was significantly related to soft tissue extension (P=.003). The authors also reported that glutathione peroxidase 1 was strongly related to local recurrence and metastasis. 20 Mosakhani et al 9 performed an miRNA microarray on metastatic and non-metastatic GCTs of the bone. They found that miR-136 and NFIB may serve as prognostic markers. These studies provided biomarkers that may be useful in predicting the clinical course of GCTs of the bone.

Two (29%) patients (cases 5 and 7), both of whom received delayed interventions for their bone lesions, died of complications of pulmonary metastasis or chemotherapy. The mortality rate (29%) in the current series was similar to that of previous reports. 10 , 11 , 22 One patient (case 5) in the current study had rapidly growing pulmonary metastases and responded poorly to surgical resection and chemotherapy. It has been previously reported that some metastatic lesions respond poorly to any form of treatment. 12

The treatments for pulmonary metastasis include close observation, chemotherapy, and surgical resection. Treatment was conservative for 4 patients in the current series because of asymptomatic metastases. One of these patients underwent lobectomy due to progression of the solitary metastasis 4 years after the detection of metastatic disease. The other 3 patients remain asymptomatic, and there has been no progression of lung metastases after a mean of 92 months of follow-up (range, 62-121 months). Viswanathan et al 7 described a patient with untreated metastatic lesions who was still alive and healthy after 16 years of follow-up. The consensus is that patients with untreated pulmonary metastasis have good long-term prognosis and positive survival rates. 5 , 7 , 8 , 10 , 11 , 13 , 17 , 22 , 23 Early intervention for primary bone lesions, conservative treatment for patients with asymptomatic pulmonary metastatic disease, and regular long-term follow-up are recommended. These patients should not receive aggressive radiation or chemotherapy because their overall prognosis and outcomes are favorable. 7

Giant cell tumors of the bone consist of neoplastic stromal mononuclear cells expressing receptor activator of nuclear factor-κB ligand (RANKL) and osteoclast-like giant cells expressing RANK. 24 , 25 Denosumab, a monoclonal antibody, binds RANKL and inhibits the RANK-RANKL interaction, thereby inhibiting the activation of osteoclast-like giant cells. 24 , 25 Denosumab has been used as an adjuvant therapy, and it can reduce surgical morbidity. 26 , 27 There were authors who used denosumab to treat metastatic lesions of GCTs of the bone and obtained good results. 25 , 28 Denosumab was not being used in this series because of it was not routinely used during the time of this study.

One limitation of this study was the small number of patients with GCT pulmonary metastases, which prevented an evaluation of the various factors predicting pulmonary metastases and long-term outcome. Another limitation was that not all pulmonary metastases were histologically verified. However, the clinical details of this series are similar to that of other reported series.

CONCLUSION

Giant cell tumors of the bone are benign but locally aggressive bone tumors with rare metastasis that occurs mostly in the lungs. The risk factors for pulmonary metastasis may include delayed treatment for bone lesions, local aggressive disease, and multiple recurrences. There is no association between metastasis and the site of the primary bone lesion. The treatment for pulmonary metastasis of GCTs of the bone is observation; however, the primary bone lesions should be cured more aggressively. The long-term prognosis and survival rate for the patients with pulmonary metastasis are favorable.

REFERENCES

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