



REVIEW

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Pulmonary metastasis of giant cell tumor of bones

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Abstract

Giant cell tumor of bone (GCTB) accounts for 5% of primary skeletal tumors. Although it is considered to be a benign lesion, there are still incidences of pulmonary metastasis. Pulmonary metastasis of GCTB may be affected by tumor grading and localization as well as the age, gender and overall health status of the patient. Patients with local recurrence are more likely to develop pulmonary metastasis of GCTB. High expression of some genes, cytokines and chemokines may also be closely related to the metastatic potential and prognosis of GCTB. The treatment of the primary GCTB is key to the final outcome of the disease, as intralesional curettage has a significantly higher local recurrence and pulmonary metastasis rate than wide resection. However, even patients with pulmonary metastasis seem to have a good prognosis after timely and appropriate surgical resection. It is hoped that with the development of novel surgical methods and drugs, pulmonary metastasis of GCTB can be prevented and treated more effectively.

Keywords: Giant cell tumor, Bone, Pulmonary metastasis

Review

Giant cell tumor of bone (GCTB) is a primary intramedullary tumor which is supposedly benign but can be locally aggressive and even metastatic [1-3]. Its name originated from the giant cells found within the tumor. Those giant cells share specific markers with osteoclasts such as tartrate-resistant acid phosphatase [4], cathepsin K [5], carbonic anhydrase II [6], calcitonin receptor [7] and receptor activator of nuclear factor- κ B (RANK) [8]. They both have bone resorption capabilities, but giant cells are significantly larger than the osteoclasts and have hundreds of nuclei [9].

GCTB account for 5% of primary skeletal tumors and 21% of all benign bone tumors [10,11]. It has the highest prevalence among the population aged between 20 and 40-years-old and has a slight female predominance [12], with the female to male ratio of 1.3 to 1.5:1.0 [13]. The most usual sites for GCT include distal femur, proximal tibia and distal radius [14-18]. The incidence of GCTs in small bones is less than 1% of all GCT cases [19,20].

Diagnosis of giant cell tumor of bone

Conventional diagnostic methods of GCTB include its clinical, radiological and histopathological manifestations. Diagnostically, typical clinical manifestations of GCTB include regional pain, swelling and occasionally history of pathological fracture [21]. Radiographs demonstrate an eccentric lytic lesion with cortical extension. Histologically, GCT consists of multiple multinucleated giant cells with strong phenotypic similarities to osteoclasts and spindle-shaped proliferative stromal cells [15,22].

More recently, the increasingly popular application of novel imaging techniques such as positron emission tomography/computerized tomography (PET/CT) has made the diagnosis of primary and metastatic GCTB more accurate [23]. Furthermore, basic research has also provided diagnostic gene markers such as P53, P63 and P73 [24,25], as well as KTN 1, NEB, ROCK1 and ZAK [26]. However, more research is needed before these biomarkers can be used in clinical practice.

Pulmonary metastasis of giant cell tumor of bone Prevalence

Although rare, GCTB can be multicentric or arise in locations where it is difficult to be surgically removed. The

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course of progression of GCTB varies and can range from local bony destruction to local metastasis. The distant metastasis and malignant transformation are extremely rare conditions [27]. Rare cases of metastases to other sites have been described in the literature. Those reported include the lung, lymph nodes [28], liver, soft tissue [29], brain, mediastinum, scalp, kidney and penis.

Based on the current literature, approximately 3% of GCTB metastasizes to the lung (Table 1). Pulmonary metastasis is very rarely discovered during diagnosis of the initial GCTB, but more frequently in cases of recurrence. The interval from the time of surgery on the primary lesion to the occurrence of pulmonary metastasis can be as little as several months or more than 10 years. However, in most cases metastases were found within three years after the surgical treatment of the initial lesion [30,31]. Based on the current literature (Table 1), approximately 3% of GCTB metastasizes to lung at certain time points after the confirmed diagnosis of primary GCTB.

Factors related to the pulmonary metastasis of giant cell tumor of bone

There is no consensus on which factors may affect the likelihood of pulmonary metastasis of GCTB. However,

several independent studies on some special types of GCTB may bring some insights into this issue. For example, Faisham *et al.* [39] have reported a pulmonary metastasis ratio of 30% in patients with grade 3 GCTB by Campanacci's classification, indicating that the tumor grading might be an important prognostic factor for the prediction of pulmonary metastasis of GCTB. Donthineni *et al.* [38] have reported a pulmonary metastasis ratio of 13.7% in patients with GCTB which occur primarily on spine, and Errani *et al.* [32] reported a higher incidence of pulmonary metastasis of GCTB located in proximal femur and distal radius, indicating that the location of primary lesion might also be a prognostic factor. However, most authors believe that there is no significant relationship between the location of GCTB and its risk of pulmonary metastasis.

Rock *et al.* [47] had reported a six-fold higher risk of lung metastasis in patients who experienced local recurrence of GCTB compared with patients with no history of local recurrence. Studies by Rock and several other authors indicate that higher risk patients with recurrent GCTB should be carefully monitored for pulmonary metastases after the appropriate treatment of the recurrent lesion (Table 2). Most studies assume that local recurrence of GCTB is a risk factor for lung metastasis.

Moreover, literature of basic research has also provided us with methods to predict the possibility of pulmonary metastasis. For example, pro-osteoclastogenic

Table 1 Some studies on pulmonary metastasis of giant cell tumors of bone

Study (Author/year)	Time of follow up	Number of patients	Ratio of pulmonary metastasis
Errani <i>et al.</i> 2010 [32]	91 (36-204) months	349	4%
Kremen <i>et al.</i> 2012 [33]	0.1-312 months	230	2%
Takeuchi <i>et al.</i> 2011 [34]	2-180 months	110	7.5%
Klenke <i>et al.</i> 2011 [35]	108 (36-233)months	118	4.2%
Viswanathan <i>et al.</i> 2010 [36]	4 months-12 years	470	1.7
Balke <i>et al.</i> 2008 [37]	60 (8-280) months	214	3.3%
Donthineni <i>et al.</i> 2006 [38]	18-126months	51	13.7%
Faisham <i>et al.</i> 2006 [39]	12-60 months	20	30%
Dominkus <i>et al.</i> 2006 [30]	3 months to 11.9 years	649	2.1%
Prosser <i>et al.</i> 2005 [40]	70 (24-214) months	137	1.6%
Su <i>et al.</i> 2004 [41]	62 (28-138) months	87	1.2%
Trieb <i>et al.</i> 2001 [42]	11 (4-43) years	47	0%
Blackley <i>et al.</i> 1999 [43]	80 (29-132) months	59	1.7%
O'Donnell <i>et al.</i> 1994 [44]	4 (2-10) years	60	0%
Kay <i>et al.</i> 1994 [45]	23-120 months	66	9.1%
Campanacci 1 <i>et al.</i> 1987 [1]	2-44 years	280	2.1%
McDonald <i>et al.</i> 1986 [46]	84 (min 24) months	146	3.2%

Table 2 Studies involving the relationship between local recurrence and pulmonary metastasis of GCTB

Study (Author/year)	Number of patients	Number of patients with pulmonary metastasis	Local recurrence
Kremen <i>et al.</i> 2012 [33]	230	5	28
Klenke <i>et al.</i> 2011 [35]	118	5	24
Errani <i>et al.</i> 2010 [32]	349	14	52
Prosser <i>et al.</i> 2005 [40]	137	22	26
Trieb <i>et al.</i> 2001 [42]	47	0	11
Blackley <i>et al.</i> 1999 [43]	59	10	12
Kay <i>et al.</i> 1994 [45]	66	6	18
O'Donnell <i>et al.</i> 1994 [44]	60	0	15
Viswanathan <i>et al.</i> 2010 [36]	470	8	13 of 24 patients with lung metastasis
Tubb <i>et al.</i> 1992 [48]			7 of 13 patients with lung metastasis
Goldenberg <i>et al.</i> 1970 [28]	218	6	5 of 6 patients with lung metastasis

Table 3 Recurrence rates after different surgical treatment of giant cell tumors of bone

Study (Author/year)	Number of patients	Wide resection	Intralesional curettage	Intralesional curettage + regional burring	Intralesional curettage + PMMA
Klenke <i>et al.</i> 2011 [35]	118	5	N/A	32	+ phenol + burrin:15
Errani <i>et al.</i> 2010 [32]	349	12	N/A	18	
Balke <i>et al.</i> 2008 [37]	214	0	140	47	+phenol: 38
Kivioja <i>et al.</i> 2008 [11]	294	12	51	N/A	22
Knochentumoren 2008 [52]	256	2	49	N/A	+phenol:69
Malek <i>et al.</i> 2006 [56]	40	N/A	N/A	33	N/A
McGough <i>et al.</i> 2005 [57]	183	N/A	46	N/A	N/A
Prosser <i>et al.</i> 2005 [40]	137	0	N/A	N/A	+burring: 21
Su <i>et al.</i> 2004 [41]	87	3	N/A	N/A	+phenol: 18
Turcotte <i>et al.</i> 2002 [55]	186	34	N/A	N/A	+phenol + burring:55
Blackley <i>et al.</i> 1999 [43]	59	N/A	N/A	12	N/A
Campanacci <i>et al.</i> 1987 [1]	280	0	27	N/A	8
McDonald 1986 [45]	146	7	N/A	34	N/A

Results from the current literature implies that the recurrence ratio of GCT is: Intralesional curettage > Intralesional curettage + regional burring > Intralesional curettage + local adjuvants + PMMA > Wide resection.

cytokines such as receptor activator of nuclear factor kappa-B ligand (RANKL), interleukin (IL)-6 and tumor necrosis factor (TNF), as well as monocyte-recruiting chemokines such as stromal cell-derived factor-1 (SDF-1) and monocyte chemoattractant protein (MCP)-1, participate in unfavorable osteoclastogenesis and bone destruction [49]. High expression of those cytokines and chemokines may help predicting the metastatic potential and prognosis of GCTB.

Treatment

Treatment of giant cell tumor of bone is still one of the most controversial and discussed issues [50]. The course of progression of metastatic pulmonary disease has been found to be as unpredictable as the primary tumor [51]. Since the incidence of pulmonary metastasis of GCTB is rather rare, there is no study on the systematic treatment of metastatic GCTB in the current literature. However, since the recurrence rate of GCTB is significantly related to its pulmonary metastasis, studies concerning treatment methods and the recurrence rate of GCTB may provide guidance for the prevention of metastasis and achieve a better prognosis.

Surgical treatment

Surgical treatment options for primary GCTB lesions include intralesional surgery and wide resection. Intralesional surgery has a higher recurrence rate but does preserve adjacent joint function. On the other hand, although wide resection may prevent metastasis, it

may seriously impair the function of adjacent joints. When curettage is performed, local adjuvants such as polymethylmethacrylate (PMMA), phenol, alcohol, cryotherapy and hydrogen peroxide have been reported to significantly decrease the rate of local recurrence and pulmonary metastasis [10,11,38,52,53]. However, some other studies [40,54] failed to find any positive therapeutic effect of these adjacent measures. In a Scandinavian Sarcoma Group multicentric study by Kivioja *et al.* [11] involving 294 patients, the recurrence rate of GCTB was 20% in patients treated with bone cement, which is significantly lower ($P = 0.001$) than the 56% recurrence rate in patients who underwent

Table 4 Number of patients with the incidence of pulmonary metastasis of giant cell tumors of bone

Study (Author/year)	Number of patients	Cases with pulmonary metastasis	Survivors at the last follow up
Kremen <i>et al.</i> 2012 [33]	230	5	4
Takeuchi <i>et al.</i> 2011 [34]	110	8	8
Errani <i>et al.</i> 2010 [32]	349	14	10*
Klenke <i>et al.</i> 2011 [35]	118	5	4
Viswanathan <i>et al.</i> 2010 [36]	470	8	8
Faisham <i>et al.</i> 2006 [39]	20	6	5
Dominkus <i>et al.</i> 2006 [30]	649	14	14
Donthineni <i>et al.</i> 2006 [38]	51	7	5
Kay <i>et al.</i> 1994 [45]	7	7	6

*3 of the 4 patients died of causes irrelevant to GCTB.

intralesional surgery with bone grafts. On the contrary, in a Canadian multicentric study of 186 patients by Turcotte *et al.* [55], filling the remnant cavity with bone cement did not significantly reduce the recurrence rate of GCTB (Table 3).

Moreover, Enneking's and Campanacci's classifications [2,58] are helpful tools for planning the initial surgical treatment. For instance, stage III GCTB is best managed with wide resection for better local control. Faisham *et al.* [39] proposed that aggressive

treatment of pulmonary metastasis is mandatory in the management of aggressive GCTB. Surgical excision of solitary and surgically-accessible lesions as well as lung metastases is now widely accepted as the treatment of choice, with an acceptable long-term survival rate [45].

Drug treatment

The anti-osteoclastic effects of bisphosphonates, along with their ability to protect bone from further resorption,



Figure 1 A 22-year-old female patient came to the orthopedic clinic complaining of continuous pain of left knee, X-ray,CT, MRI and bone scan tests found a sub-articular lucent lesion with clear boundaries on the left distal femoral bone.

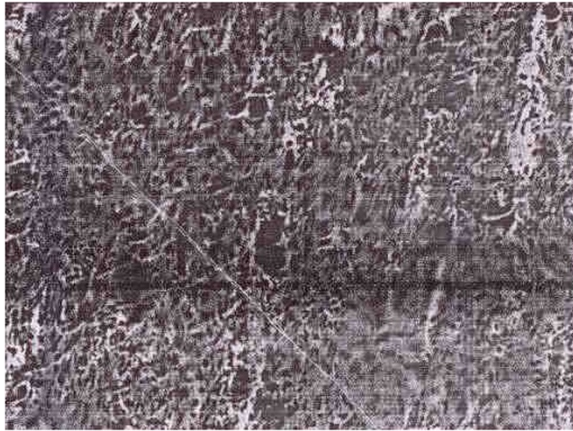


Figure 2 Pathological examination was fine needle biopsy confirmed it was giant cell tumor. Local curettage and bone grafting was performed by the local hospital.

make bisphosphonates potential candidates for the treatment of GCTB, and studies have confirmed their efficacy [59]. Balke *et al.* [37] examined clinical and radiological outcomes of treatment with amino bisphosphonates on 25 cases of aggressive primary, recurrent and metastatic GCTB derived from four European centers. Most inoperable sacral or pelvic tumors did not increase in size and no further recurrence or metastasis was observed in patients with recurrent GCTB. Lung metastases did not increase in size or number following treatment, suggesting that bisphosphonates may be useful against the progression of metastatic GCTB lesion in lung.

Denosumab, a fully human monoclonal antibody that specifically inhibits normal and tumor-associated bone lysis by preventing RANKL-mediated formation and activation of multinucleated osteoclasts or giant cells from RANK-positive mono-nuclear preosteoclasts and

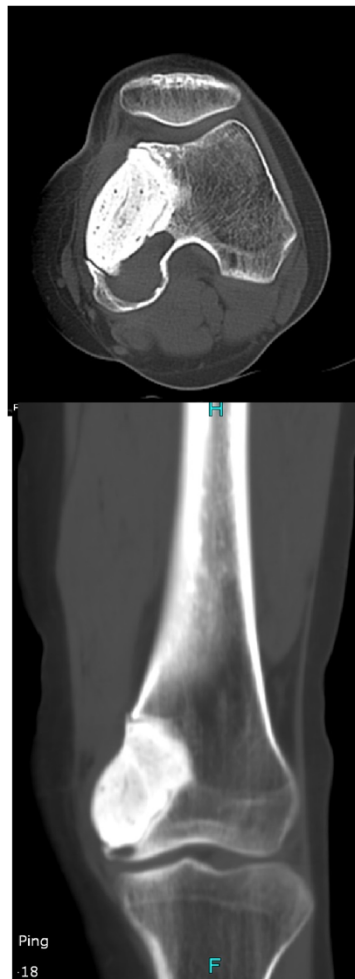


Figure 3 18 months after the first surgery, CT and bone scan found local recurrence was found at follow-up visit.



Figure 4 She was treated with *en bloc* resection under the aid of computer navigation under intraoperative CT scan, and the cavity was filled with bone cement. Intraoperative pathological exam confirmed the recurrence of GCTB.

macrophages [21], has been proved to be able to reduce the number of RANK-positive giant cells and proliferative stromal cells [15]. In the study of Thomas *et al.* [60], 30 out of 35 (86%; 95% CI 70 to 95) of

evaluable patients had a positive tumor response after the treatment of denosumab. It is likely a novel and effective method with great potential in the treatment of GCTB [61].

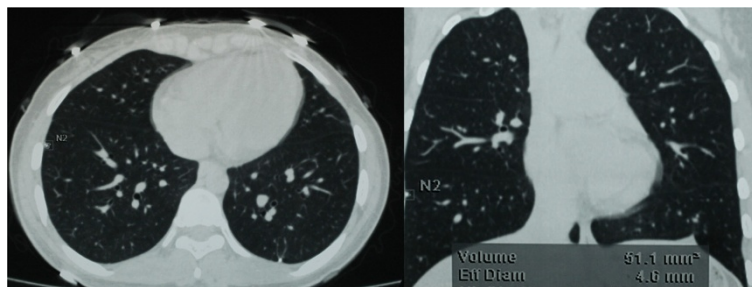


Figure 5 34 months after the first surgery, multiple nodules were found by CT scan in both of her lungs on a follow-up visit.

Prognosis

For lung metastasis, appropriate surgical resection such as metastasectomy, wedge resection or lobectomy should be carried out if it is possible to prevent progressive pulmonary dysfunction [30,62]. Because pulmonary metastases are rare and timely surgical and chemotherapeutic treatment is usually successful (Table 4, see Figures 1, 2, 3, 4, 5 and 6 for an example case), we believe the potential for metastases should not by itself be an indication for wide resection of primary tumors.

Conclusions

In conclusion, GCTB is normally considered a benign bone tumor. However, it may occasionally metastasize to vital organs such as the lung. The prognosis can be successful with timely and appropriate surgical treatment and chemotherapy. With the development of novel surgical methods and application of new drugs, most patients with GCTB can still achieve successful treatment results.



Figure 6 At the last follow-up visit 40 months after the first surgery, Ct scan showed that the patient was alive with the disease, complaining of no trouble with breathing.

Abbreviations

CT: computerized tomography; GCTB: Giant cell tumor of bone; IL: interleukin; MRI: magnetic resonance imaging; MCP: monocyte chemoattractant protein; PMMA: polymethylmethacrylate; PET/CT: positron emission tomography/computerized tomography; RANK: receptor activator of nuclear factor- κ B; RANKL: receptor activator of nuclear factor kappa-B ligand; SDF: stromal cell-derived factor-1; TNF: tumor necrosis factor.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Dr A.M searched for the papers, extracted the research data from those papers and drafted the manuscript. Dr X.N checked the structure of the manuscript, provided the patient file and figures of the patients he has treated. Both authors read and approved the final manuscript.

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