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### Case Report

# Multifocal, Metachronous Giant Cell Tumour in a 59-Year- Old Male Patient with Rare Localisation: A Case Report

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### Abstract

Giant cell tumours (GCT) of bone are classified as benign or intermediate neoplasm and affect long bones in most of the cases. However, giant cell tumour of bone represents about 5% of primary bone tumours, but occurrence of multifocal GCT is rare. Multifocal GCTs occur in less than 1% and metastatic spread of these lesions is very uncommon. Further, reports of multifocal, metachronous GCTs are very rare in literature.

Herein, we present a case of a 59-year old male patient, who suffered from multifocal, metachronous GCT, which involved the skull, the sacrum, lung and abdomen.

Due to the fact that this case is rather rare, right diagnosis is getting complicated because metastatic lesions of the masked primary giant cell tumour of bone could be misunderstood and may lead to other ways of therapy. In conclusion the present case report emphasizes the possibility of a multifocal GCT of bone as a possible differential diagnosis for multiple osteolytic lesions with metastatic spread to lungs, abdomen or other regions.

### INTRODUCTION

As described by the WHO the definition of Giant cell tumour (GCT), or also called Osteoclastoma, is a benign, locally aggressive neoplasm which is composed of mononuclear cells interspersed with large, osteoclast-like giant cells [1]. The GCT of bone represents about 5-8% of primary bone tumours [1]. It can't be exactly distinguished, whether it is a benign or malignant neoplasm of bone, due to its low rate of metastatic spreading, but rather

aggressive growth. Therefore it is declared as an "intermediate" bone tumour, low grade or potentially malignant neoplasm [2-4]. GCTs develop cumulatively in the second to fourth decade of life with a slight predominance in female patients [1]. The GCT is mostly located in long bones and shows highest occurrences in distal femur, proximal tibia or the sacral bone. GCT develops in an epiphyseal area in most of the cases and carries the possibility of spreading into the intra-articular space. In young adolescents a metaphyseal location is also possible. The occurrence of

multifocal GCT is very rare and so is metastatic spreading, although studies mention possible pulmonal metastases in some rare cases [1].

Pain is usually the first symptom, whereas local swelling and a palpable mass are not usually found at onset. In some rare cases, the tumour was discovered by radiological imaging before the appearance of any symptoms. Some female patients reported about first symptoms during pregnancy [3].

In radiological imaging GCTs express as excentrical osteolysis with a sharp margin, which can also reach into subchondral regions and even affect the intra-articular space [4].

Because of locally aggressive growth, which can even lead to destruction of the corticalis and affliction of soft tissue, and the relatively high recurrence rate, which is reported as 25% of cases, a quick surgical treatment and stabilisation through bone craft or bone cement is obligatory [1]. Radiation therapy is just needed in selected cases if resection is incomplete [5].

Herein we present a rare case of multifocal GCT in a 59-year-old male patient, the diagnostic and therapeutic steps towards correct treatment.

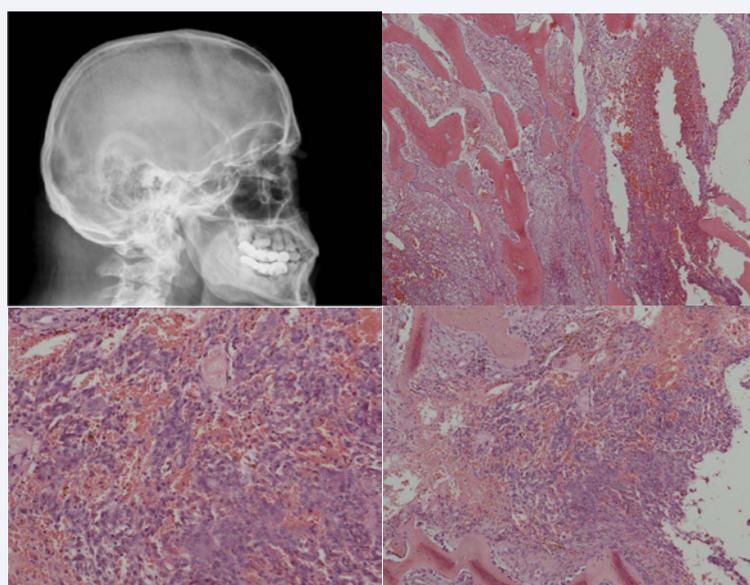
## CASE PRESENTATION

A 59-year-old male patient presented in February 2012 at our department with an osteolytic lesion in the sacral bone. At first it was considered to be a metastasis from a lung tumour, which was treated by lobectomy in 2007 after the patient appeared with haemoptysis. CT-scans showed a 5.8 x 6.5 x 5.6cm expansive lesion in the lower segment of the right lung, suspected to be a carcinoma. Histological it was determined to be a malign mesenchymal and epithelial tumour, which consists of components of pleural tumour and an adenocarcinoma, also a high amount of giant cells was reported.

In 2009, the patient reported swelling of the right calvaria and the x-rays showed an osteolytic lesion in the frontal bone of the skullcap with a diameter of 4 centimetres (Figure 1a). It was first considered as metastasis, but later on found to be a GCT (Figure 1b-d), which was resected at the department of neurosurgery.

As mentioned before, the patient presented at our department in February 2012 with back pain and paraesthesia in gluteal and genital region, ongoing since two weeks and furthermore a complex history of multiple bone lesions and tumours. MRT and CT-scan of the sacrum revealed an osteolytic lesion with the size of 8 x 5 x 4 centimetres located in the region of S1 and S2. There was also a lesion found in right processuscostalis of L4 with an extend of 1,5 x 1,6 centimetres and one in the ala ossisilli (6 x 9 millimetres), which led to the differential diagnosis of multiple metastatic lesions (Figures 2 a&b). Therefore it was decided to perform a radiation therapy for the metastasis in the sacral bone, but also to do a CT-guided biopsy and a bone scan.

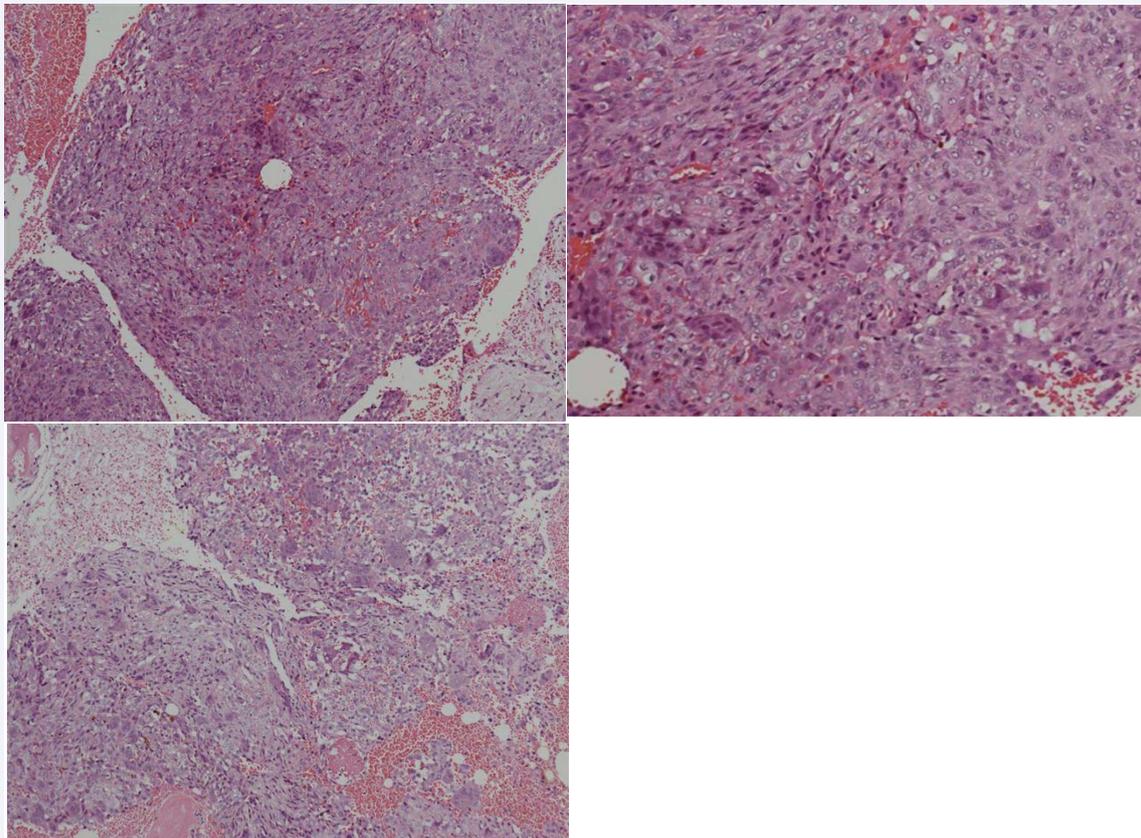
The first histological investigation from the material out of biopsy just revealed giant cells and fibrin, but could not ensure a definite diagnosis. Radiation was cancelled due to the possibility of a primary specimen and a second, open biopsy was done. The histological diagnosis from the second biopsy revealed proliferation of giant and mononuclear cells with mitoses figures, haemorrhagia and necrosis and destruction of bone with osteoid layers (Figure 3a-c). Due to the histological report and the clinical signs the diagnosis of regressive transformed and necrotic GCT was brought up and was also determined in later histology. Therefore, the specimen of the lung from 2007, which was thought to be a carcinoma was questioned and re-evaluated together with the GCT from osfrontale. The differential diagnosis of metastatic GCT to the lung, due to the masked primary lesion, was brought up. Nevertheless, due to the fact of high recurrence rate of GCTs and its multiple locations, but low progression of



**Figure 1** (a-d) Osteolytic lesion in the frontal bone of the skullcap. H&E stained section of the specimen from the skullcap showing the histological pattern of a GCT.



**Figure 2** (a&b) MRI of the sacrum showing a massive infiltration of the bone with destruction of the cortex.



**Figure 3** (a-c) H&E stained section of the specimen from the sacrum showing the histological pattern of a GCT.

size and the not given affection of function, it was decided to start systemic therapy with RANKL-inhibitor Denosumab.

In re-evaluation of CT-scans from February 2012 a lesion (2 x 1.7 centimetres) was found in the left mesenterium and a biopsy was done. The tumour of the abdomen was resected in toto and revealed the histological diagnosis of a secondary GCT, which was associated with the GCT of the sacrum. After a follow-up of 6

months a new lesion fronto-parietal was discovered. In November 2012 the patient presented with severe pain in the lower back. A CT-scan of the sacrum showed progression of disease, therefore it was decided to perform a local radiation therapy as well as to perform palliative chemotherapy. Although the therapy with Denosumab was started, the patient died of disease 14 months following diagnosis.

## DISCUSSION

GCT was first described in 1818 by Cooper and Travers [6]. As mentioned before the GCT is known as a benign lesion of the bone with an aggressive local growth. GCT is usually a monostotic lesion, but there have also been multicentric (polyostotic) forms reported in the literature. Dahlin et al [7]. Presented a study of 407 patients with just three occurrences of multicentric GCT. Multifocal GCT can present as synchronous or metachronous form with a latent period between development of the first and second lesion of at least up to 20 years [7,8].

Further we can differ between malignant and benign metastasizing GCTs. The malignant GCT can further be divided in primary and secondary malignant tumours. On the one hand, the primary form (1 to 3% of all GCTs) is malignant from the onset, on the other hand, the secondary form (5 to 10% of all GCTs) develops from a benign form during recurrence, or through malignant transformation while radiation therapy.

Benign metastatic GCTs (described in 1 to 3% of all GCTs, and up to 6% of recurrent GCTs) show the same histology as the nodules found in other organs, mostly the lung. This phenomenon is explained through tumour embolization of local vessels and for that the nodules are often found as implants and not as true metastases [8].

Histological it is known that the tumour does not consist of giant cells alone, but also of mononuclear precursor cells to the giant cells. Mononuclear histiocytic cells and multinucleated giant cells both express the CD64-Antigen and for that both are believed to derive from the monocytic-histiocytic system. The finding of multinuclear giant cells between mononuclear cells without any nuclear atypia is not enough for diagnosis of GCT. The differential diagnoses, as aneurysmal bone cysts or a brown tumour in hyperparathyroidism, have to be crossed out through precise details regarding radiological imaging, localisation and age of the patient [9].

For that the differential diagnosis is usually based on radiological appearance. GCT demonstrates as an eccentric local bone lysis, associated with a narrow zone of transition and lacking surrounding sclerosis [10].

Another differential diagnosis, which has to be crossed out, is Paget's disease. Murphey et al [10]. Describes the possibility of multiple GCTs associated with Paget's disease. In this case the GCTs occur mainly in facial region and sometimes in the spine, extremities are often not affected.

The primary therapy for GCT is resection in a wide margin. The main problem with that is the rather high recurrence rate. Szendrői [7] listed the recurrence rate of several different studies.

With no adjuvant treatment the recurrence rate reaches from 30% (Campanacci et al [6].) to 56% (Lausten et al. [10]). In more recent studies, with adjuvant chemotherapy or radiation therapy, the recurrence rate reveals a better result, 8% (Malawar and Dunham [11]) to 34% (McDonald et al [12]).

In some cases RANK/RANKL-antagonist Denosumab is used to either avoid radical surgery or in a neoadjuvant manor, to reduce pain and size of tumour. This new way of therapy promises new multimodal possibilities for the treatment of GCT [13]. Nevertheless the patient in the current case showed progression of disease during mono-modal therapy.

potential differential diagnosis	radiological signs	localisation	age
<b>GCT</b>	Eccentric local bone lysis, associated with a narrow zone of transition and lacking surrounding sclerosis.	Mostly located in long bones with the highest occurrences in distal femur, proximal tibia or the sacral bone.	Second to fourth decade of life.
<b>aneurysmal bone cyst</b>	radiographs demonstrate sharply defined, expansive osteolytic lesions, with thin sclerotic margins.[14]	Eccentrically located in the metaphysis of long bones with highest occurrences in tibia, fibula and femur. [15,18]	80% under age of 20.[16]
<b>brown tumour in hyperparathyroidism</b>	Defined, lytic lesions with reactive bone tissue. Cortex may be thinned and expanded, but no penetration.[17]	ribs, clavicles, pelvis, and mandible.[18]	55-75 year, typically women.[19]
<b>GCT associated with Pagets disease</b>	Osteolytic regions which are later followed by coarsened trabeculae and bony enlargement. Sclerotic changes occur much later [22].	Mainly in facial region, seldom in spine, extremities usually not affected.	up to 4% of individuals over 40 and up to 11% over the age of 80. [20]

## CONCLUSION

In conclusion the presented case is very rare and has relevance in differential diagnosis. The patient developed multifocal, metachronous GCTs, but he also showed signs of benign metastatic GCTs. He developed pulmonary metastases, which occur in just 1 to 2% of cases and abdominal metastases, which have not been mentioned in literature yet [21,22]. Additionally the GCT was located in facial region and the sacral bone, which are quite rare localisations. Because of that, Paget's disease has to be ruled out. Our patient did not show any of the typical osteolytic lesions in the long bones, neither was there any sign in scintigraphy. Because of the multiple lesions and their diffuse growth, resection was not possible. We decided to treat the patient with RANK/RANKL-antagonist Denosumab. RANKL (Receptor Activator of NF-κB Ligand) is a mediator of osteoclast formation, function, and survival and therefore of bone tissue metabolism. Denosumab, a fully human monoclonal antibody, binds and inhibits RANKL, thereby prevents activation of its receptor RANK, which is found on osteoclasts and osteoclast precursors and therefore decreases the catabolic effects on bone tissue [23].

Denosumab reveals clinical benefit, either in reduction of pain or improved functional status, in up to 90% of cases. Due to the fact that this case is rather rare, right diagnosis is getting complicated. Metastatic lesions of the masked primary giant cell tumour of bone could be mistaken and may lead to other ways of therapy. The present case emphasizes the possibility

of a multifocal GCT of bone as a possible differential diagnosis for multiple osteolytic lesions with metastatic spread to lungs, abdomen or other regions.

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