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# Histologically Confirmed Brain Metastasis Arising From Giant Cell Tumor of Bone: an Uncommon Entity and a Challenging Condition

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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**Patient:** Male, 38-year-old
**Final Diagnosis:** Giant cell tumor of bone
**Symptoms:** Seizure • tremor
**Clinical Procedure:** —
**Specialty:** Neurosurgery • Oncology • Orthopedics and Traumatology

**Objective:** Unusual clinical course

**Background:** Giant cell tumors of bone (GCTBs), while classified as indolent, are characterized by their locally aggressive nature and their ability to form metastases in rare cases, mainly in the lungs. To our knowledge, this case is the third reported case of GCTB central nervous system involvement in the literature.

**Case Report:** We report the exceptional case of a 39-year-old patient with no significant medical history who presented with a GCTB of the left distal femur, treated with preoperative denosumab and surgical resection with massive prosthetic reconstruction. Fifteen months later, the onset of tremors and a partial seizure revealed a right parietal brain metastasis, histologically confirmed as a secondary site of GCTB. Management included surgical excision of the brain lesion, followed by close monitoring with brain MRI, without adjuvant radiotherapy. Before the present report, only 2 cases of GCTB metastasis involving the central nervous system have been reported, including an intramedullary thoracic lesion and bilateral parietal lesions.

**Conclusions:** This case is the third reported case of GCTB metastasis with central nervous system involvement, highlighting the importance of prolonged follow-up and an individualized multidisciplinary approach for these tumors, which usually metastasize to the lungs. Although these 3 case reports help to characterize this rare condition of secondary central nervous system involvement in GCTBs, they do not justify routine brain imaging or a set standard for follow-up strategies; instead, a multidisciplinary and individualized approach is recommended. The patient is currently in clinical and radiological remission.

**Keywords:** Sarcoma • Brain Neoplasms • Rare Diseases

**Full-text PDF:** https://www.amjcaserep.com/abstract/index/idArt/953858





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## Introduction

Giant cell tumors of bone (GCTBs), while classified as indolent, are characterized by their locally aggressive nature and their ability to form metastases in rare cases, mainly in the lungs. Lung metastases from bone GCTBs are considered rare (5%-10% of cases), with identified risk factors including age at diagnosis, axial location of the primary tumor, and local recurrence, highlighting the importance of early and appropriate management [1]. To our knowledge, this case is the third reported case of GCTB with central nervous system involvement in the literature.

## Case Report

We report the case of a patient in his thirties, a maintenance technician in the automotive manufacturing industry, with no relevant personal history, who consulted for progressive pain in his left knee over the past year without systemic symptoms or deterioration in general condition. He had a personal history of a rotator cuff tear in his right shoulder. A standard radiograph revealed a lytic lesion of the left femur, followed by a CT scan and magnetic resonance imaging (MRI), showing a distal osteolytic lesion of the left femur, with a mixed tissue and cystic component, invading the soft tissues and associated with a fracture line in the intercondylar notch (**Figure 1**).

A systematic extension assessment with chest CT scan did not reveal any secondary GCTB lesion. These radiological findings suggested a GCTB with a secondary aneurysmal bone cyst. Surgical biopsy confirmed the diagnosis, with an expert review by the French network of specialist pathologists. The morphological characteristics and immunohistochemical profile were typical of a GCTB, with minimal aneurysmal remodeling and no criteria for malignant (sarcomatous) transformation. The case was discussed at a multidisciplinary sarcoma tumor board meeting, and preoperative denosumab was started. Denosumab 120 mg was administered subcutaneously as a loading dose on Day 1, Day 8, Day 15, and Day 28, followed by administration every 28 days for 3 additional cycles. Daily oral supplementation with 500 mg calcium and 440 IU of cholecalciferol was administered starting on Day 1. Denosumab was well tolerated, with no dental adverse effects and no hypocalcemia. Neoadjuvant treatment led to peri-lesional ossification indicating a good radiological response and improvement in knee pain. Resection of the distal femur with simultaneous reconstruction using a massive prosthesis was performed.

Fifteen months after surgery, the patient developed intermittent tremors in his left hand, followed by a partial convulsive epileptic seizure. An emergency brain scan revealed a right frontoparietal lesion with perilesional edema and mass effect on the right

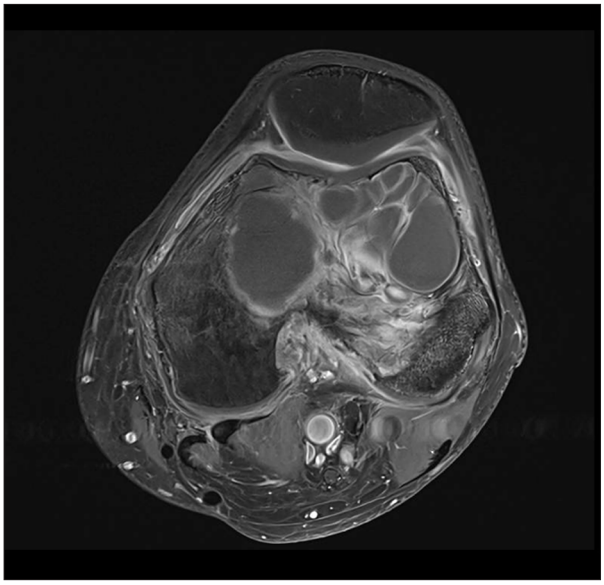

**Figure 1.** Preoperative T1- weighted MRI showing an osteolytic lesion of the left femur, with a mixed tissue and cystic component, invading the soft tissues and associated with a fracture line in the intercondylar notch. MRI, magnetic resonance imaging.

lateral ventricle suspected to be a secondary lesion on brain MRI (**Figure 2A**). A complementary CT scan ruled out the presence of other suspected GCTB lesions, including in the thorax, and the multidisciplinary tumor board meeting advised resection of this isolated symptomatic brain lesion. Neuronavigation-guided surgery based on preoperative MRI, with intraoperative ultrasound imaging of the lesion, was performed after a retrocentral corticotomy, allowing macroscopically complete resection. Surgical excision of the brain lesion revealed a right parietal metastatic site of a primary bone GCTB, confirmed by histological and immunohistochemical analysis (expressing H3F3A protein G34W mutant and P63, Ki67 assessed at 20%) without sarcomatous dedifferentiation. A slight motor deficit involving extension of the left hand was noted following surgery, which resolved quickly.

This exceptional presentation of a unique cerebral metastasis of GCTB was discussed at a national tumor board meeting to assess the need for additional treatment. Twice-monthly monitoring using cerebral MRI without additional radiotherapy was advised (**Figure 2B**). The patient is currently in remission and shows no signs of radiological or clinical relapse. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

## Discussion

We report the case of a patient previously treated surgically for GCTB who later developed a resected secondary lesion





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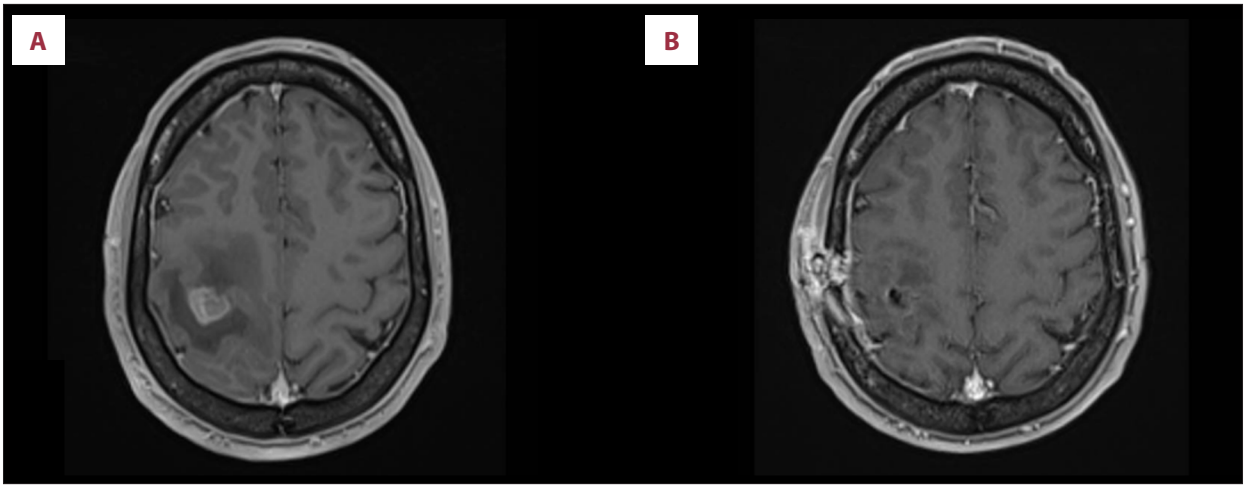


**Figure 2.** (**A**) Preoperative T1-weighted brain MRI with gadolinium contrast: single intraparenchymal tissue lesion on the right central region, with clear vasogenic edema reaction with a suspected secondary origin. (**B**) Postoperative T1- weighted brain MRI with gadolinium contrast: post-surgical remodeling with no signs of recurrence. MRI, magnetic resonance imaging.

**Table 1.** Comparison of the 3 reported cases of central nervous system (CNS) metastasis arising from giant cell tumors of bone (GCTB).

| Reported cases | Age at diagnosis of GCTB | Sex | Primary tumor location | Pulmonary metastasis | Site of CNS involvement | Time to CNS metastasis | Treatment strategy | Clinical outcome |
|---|---|---|---|---|---|---|---|---|
| Ozaki et al 2011 [7] | 26 | Female | Proximal phalanx of the hand | 2 years from initial diagnosis | Intramedullary thoracic spinal cord tumor between T12 and L1 | 16 years from initial diagnosis | Excisional biopsy with Th12-L1 laminectomy | Palliative radiation therapy (30 Gy/10 fr) from Th9 and L3 at local relaps |
| Wong et al 2014 [6] | 51 | Female | Left proximal tibia | 12 years from initial diagnosis | 2 lesions, 1 in each parietal lobe | 20 years from initial diagnosis | Bilateral craniotomies for resection of the 2 lesions followed by 4 cycles of denosumab | Mild upper extremity weakness with no relapse |
| Current case | 39 | Male | Left distal femur | Absence | Retrocentral right single lesion | 1.5 years from initial diagnosis | Surgical excision without adjuvant therapy | Transient motor deficit affecting left hand with no relapse |

in the central nervous system. The postoperative follow-up procedures, in particular the opportunity for additional irradiation after brain surgery, were discussed at a national multidisciplinary tumor board meeting. After considering the various opinions, the team decided to monitor the postoperative cavity with MRI every 3 months and not to give adjuvant radiotherapy. This individualized multidisciplinary decision balanced the patient's complete surgical resection, the rarity of intracranial GCTB metastasis, the uncertain benefit of postoperative radiotherapy, and the recognized but uncommon risk of radiation-associated malignancy. The significance of this case report to the literature consists of the histological characterization of an isolated lesion of the central nervous system without associated secondary pulmonary involvement.

American and European recommendations on initial staging in localized or metastatic situations suggest that, in addition to local multimodal imaging (CT scan, MRI), a chest CT scan should be performed. The monitoring assessment consists of local multimodal imaging, followed by CT scans every 6 to 12







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months for 4 years, then annually and at clinical request. No brain imaging is recommended in the guidelines for localized disease or in situations of metastatic presentation upon diagnosis or at relapse as it is a very rare condition. There is no consensus on the role of denosumab in neoadjuvant or adjuvant settings. However, in the event of a lesion (metastatic or not) or an unresectable lesion that cannot be treated with curative intent, denosumab is the preferred primary treatment. Radiotherapy is reserved for unresectable or progressive lesions that do not respond to denosumab [1,2].

Although secondary GCTB lesions are uncommon (below 10%), their preferred location is the lungs; this is widely documented in the literature [3]. Cephalic locations of GCTBs consist mainly of primary or secondary bone lesions of the cranial vault or skull base. A systematic review identified 24 published cases of GCTB of the clivus, with patients aged between 9 and 62 years at diagnosis, with clinical manifestations including headaches and paralysis of the cranial nerves, notably the abducens nerve. Treatment consists of subtotal resection followed by radiotherapy (52% of cases) or denosumab, with an average recurrence rate of 37% and 2 cases of malignant transformation, suggesting the limited efficacy and potential risks of radiotherapy. This review highlights the potential benefit of denosumab for long-term tumor control [4]. A review of the literature on occipital GCTBs, which account for less than 1% of cases, shows that they mainly affect adults, with a slight predominance in women. Among the 21 cases reported, complete surgical resection reduces the risk of recurrence. Long-term follow-up with MRI seems essential due to the unpredictable behavior of these tumors [5].

Only 2 cases of GCTB metastasis involving the central nervous system have been reported: 1 intramedullary thoracic lesion and 1 case with bilateral parietal lesions. A middle-aged female patient developed a local tibial recurrence and pulmonary metastasis 10 years after initial surgery, followed by bilateral parietal lesions 20 years after initial surgery, which were histologically confirmed as GCTB brain metastases. After surgical resection and treatment with denosumab, there were no signs of relapse, but pulmonary progression required surgical resection [6]. The other reported case of confirmed central nervous system involvement was a thoracic intramedullary spinal cord tumor in a young adult patient with a history of pulmonary metastases from GCTB [7]. Although these 3 case reports help to characterize this rare condition of secondary central nervous system involvement in GCTBs, they do not justify routine brain imaging or set a standard for follow-up strategies; instead, they illustrate that a multidisciplinary and individualized management strategy is needed (**Table 1**).

Radiotherapy is generally avoided in the treatment of GCTBs due to the possible increased risk of secondary malignant transformation. Retrospective studies show that a few patients develop a secondary malignancy, which can occur even years after treatment. These post-radiation sarcomas are associated with a poor prognosis, with a 5-year survival rate lower than that of primary malignant forms. Radiotherapy is therefore only advised for inoperable cases or critical locations (spine, sacrum), where the benefits outweigh the risks. For surgically accessible GCTBs, however, complete resection with reconstruction remains the standard treatment, combined if required with local treatments (phenol, cement), to minimize the risk of recurrence or malignant transformation [3,8]. Asian studies show that the majority of secondary malignant transformations occur without a history of radiotherapy, suggesting additional ethnic or biological factors. Although radiotherapy offers good local control (up to 85%), its use must be considered on a case-by-case basis, respecting the precautionary principle and favoring alternative treatments (surgery, denosumab) whenever possible to minimize the risk of post-radiation sarcoma [9].

## Conclusions

Central nervous system metastasis from a GCTB is a rare condition requiring individualized multidisciplinary collaboration to define the optimal treatment strategy and follow-up management. Although a single case cannot be the basis for the development of general recommendations, this report should lead to caution in interpreting diagnostic and prognostic implications, as well as to increased awareness during follow-up.

### Institution Where Work Was Done

Institut de Cancérologie de Lorraine, Vandœuvre-lès-Nancy, France.

### Patient Consent

The patient agreed to the publication of this case report and participated in data collection to ensure the accuracy of the report. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

### Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.





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