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Primary Malignant Giant Cell Tumor of Bone with Metastasis: A Case Report and Literature Review

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Learning Point of the Article:

Primary malignant transformation in a giant cell tumor of bone is an extremely rare event, and its early diagnosis is pivotal in determining the appropriate management and prognosis.

Abstract

Introduction: Malignant giant cell tumor of bone (GCTB) is a very rare tumor, especially the primary type of it. We report a case of a young female who was diagnosed with a primary malignant giant cell tumor, in addition to a literature review of the previously reported cases. This case report aims to highlight the importance of high clinical suspicion and comprehensive workup to detect malignancy in giant cell tumors. We also review and add another case to the medical literature to help better understand the behavior of this rare tumor.

Case Report: A 30-year-old African American female presented with left knee pain. Imaging showed a cystic bone lesion of the left proximal tibia, which was found to be consistent with a primary malignant giant cell tumor on biopsy. She started neoadjuvant chemotherapy (methotrexate + doxorubicin + cisplatin); however, she only tolerated one cycle, and then she underwent a radical resection of the left proximal tibia with endoprosthetic reconstruction. She had multiple hospitalizations later, and she was found to have significant pulmonary and spinal metastasis. Eventually, she decided to resume chemotherapy due to her worsening disease, and she completed four cycles of doxorubicin and cisplatin with a recent plan to switch to regorafenib given her refractory disease.

Conclusion: Diagnosis of primary malignant GCTB can be very challenging. It is always important to seek an expert opinion given the rare nature of this tumor. Early detection is very important to establish the appropriate treatment.

Keywords: Giant cell tumor of bone, malignant, primary, secondary.

Introduction

Giant cell tumor of bone (GCTB) is a known benign locally aggressive bone tumor that comprises approximately 5%–6% of all primary bone tumors [1,2]. Malignancy in giant cell tumors is generally rare (occurs in about 1.8% of cases) [1], especially primary malignant giant cell tumor (PMGCTB), which is considered to be extremely unusual, whereas secondary malignant giant cell tumor (SMGCTB) seems to be more common, and it usually presents following radiotherapy or surgical treatment [3]. GCTB can rarely metastasize in about 2% of the cases [4] with the lungs being the most common site [2], and even the benign version of GCTB has the ability to metastasize to the lungs too [1].

Case Report

A 30-year-old African American female with no significant past medical history presented to the University Medical Center of Southern Nevada (UMC) with left knee pain for about 2 years that got worse over a few weeks. Before the presentation, she had an outpatient X-ray done showing a left knee bone lesion. She

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Author's Photo Gallery


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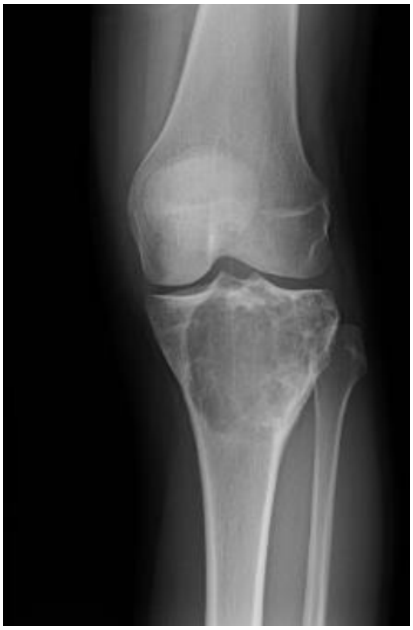

Figure 1: Left knee X-ray on initial presentation shows a cystic bone lesion in the proximal tibia.

was also evaluated by an oncology outpatient, but no further workup was done by that time.

On admission, the physical examination was only remarkable for tenderness over the left proximal tibia and mild pain with range of motion of the left knee. All vital signs were within normal limits.

X-ray of the left knee (Fig. 1) showed a cystic bone lesion of the proximal tibia. Magnetic resonance imaging (MRI) with and without contrast (Fig. 2) revealed a large complex intramedullary mass of the proximal tibia without evidence of cortical destruction or extraosseous soft-tissue invasion, and the findings were consistent with a giant cell tumor. Chest X-ray (Fig. 3) was unremarkable with no signs of metastasis.

Computed tomography (CT) guided core needle biopsy of the lesion was done, histopathologic examination (Fig. 4) showed several cores of haphazardly arranged spindle to slightly epithelioid cells with enlarged irregular nuclei, mitotic figures were readily identified, immunohistochemical staining was positive for vimentin and CD68 with focal faint staining for smooth muscle actin. The aforementioned findings were all found to be consistent with a poorly differentiated neoplasm. The case was sent to the Mayo Clinic in Rochester, Minnesota, for expert opinion. The report came back with a diagnosis of a malignant GCTB. The H3 G34W mutation was positive which supported the diagnosis of a giant cell tumor, and the presence of several atypical cells and atypical mitosis and apoptosis supported the malignant version of the tumor.

The patient was discharged from the hospital after the biopsy was done and recommended to follow up outpatient with medical and orthopedic oncology. She was started on a MAP regimen (methotrexate + Adriamycin "doxorubicin" + platinol "cisplatin") and admitted to UMC twice for high-dose methotrexate. She completed only one round of chemotherapy and then opted to stop due to severe side effects. Four months following her initial presentation, she underwent an elective radical resection of the left proximal tibia with endoprosthetic reconstruction (Fig. 5), peroneal nerve neurolysis, and medial gastrocnemius rotational flap. Intraoperative biopsy was consistent with malignant giant cell tumor with margins negative for tumor or malignancy.

CT chest without contrast 1 year following her initial presentation showed multiple scattered bilateral sub-6 mm pulmonary nodules; however, those nodules were not active on a positron emission tomography scan.

Twenty months following her initial presentation, she presented to UMC with severe back pain radiating to her right lower extremity. CT of the lumbar spine without contrast showed an ill-defined partially sclerotic lesion involving the left L2 vertebral body with pathologic fracture with adjacent epidural hyperdense material concerning malignancy with epidural extension, there was severe spinal canal stenosis at the level of L2. MRI with and without contrast (Fig. 6) revealed a mass within the L2 and L3 vertebral bodies concerning osseous metastatic disease, in addition to enhancing mass within the spinal canal encasing the spinal nerve roots and possibly the conus medullaris from L1 through L3. She underwent a lumbar laminectomy of L1-3 for extradural tumor removal with instrumentation and fusion of L1-4. Intraoperative biopsy of

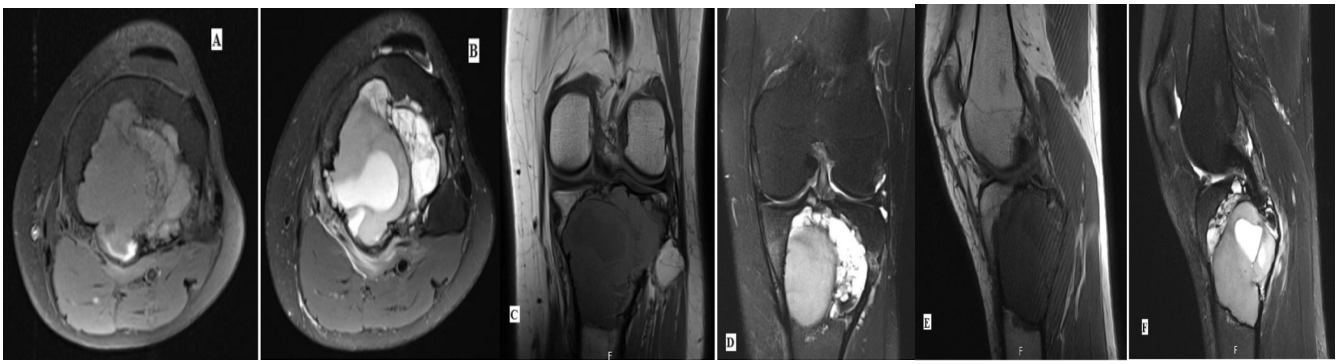

Figure 2: Magnetic resonance imaging with and without contrast of the left knee on initial presentation: (A) (T1 – axial view), (B) (T2 – axial view), (C) (T1 – coronal view), (D) (T2 – coronal view), (E) (T1 – sagittal view), (F) (T2 – sagittal view).

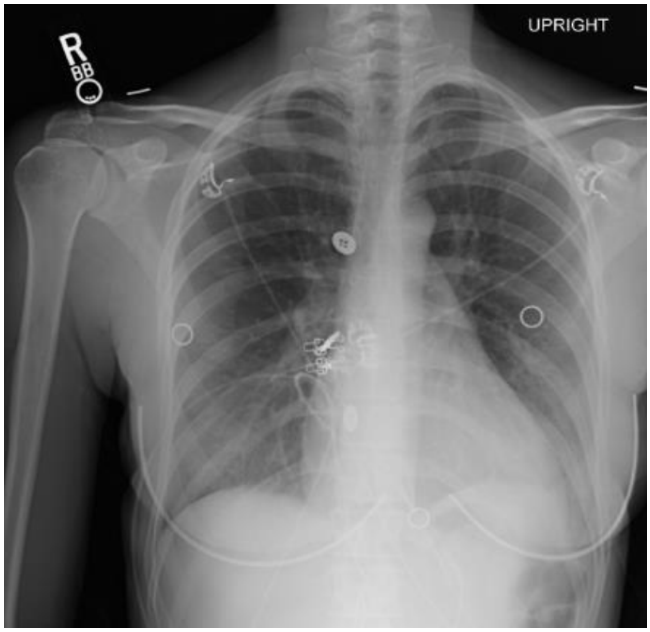

Figure 3: Chest X-ray on initial presentation, normal appearance with no signs of metastasis.

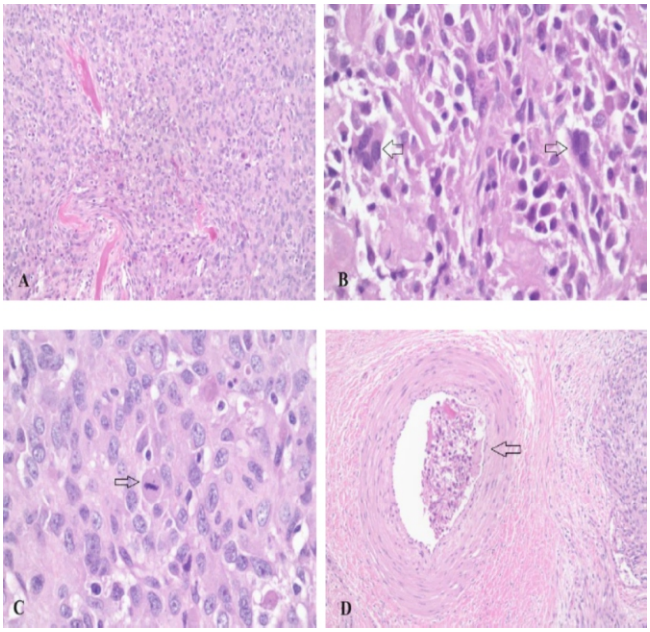

Figure 4: Primary malignant giant cell tumor H&E stain [A] hypercellularity, [B] multinucleated giant cells [arrows], [C] mitotic figure [arrow], [D] vascular invasion [arrow]).

the right L2 extradural mass was consistent with metastatic malignant giant cell tumor. No malignancy was identified on the posterior lamina's biopsy. Repeat CT chest without contrast (Fig. 7) during the same hospitalization showed worsening metastatic disease with over 20 pulmonary nodules/masses noted.

The patient had multiple hospitalizations afterward, most of them due to severe back and bilateral lower extremity pain, one of them being for worsening shortness of breath when she was found to have bilateral pulmonary emboli. Due to her worsening clinical status, she finally decided to restart chemotherapy. She was evaluated at USC (University of Southern California) for a second opinion, and she was started on the following regimen (cisplatin 75 mg/m2 IV on day 1 + doxorubicin 25 mg/m2 IV on days 1–3). She completed four rounds so far, and the most recent plan is to switch her to regorafenib given her refractory and metastatic disease.

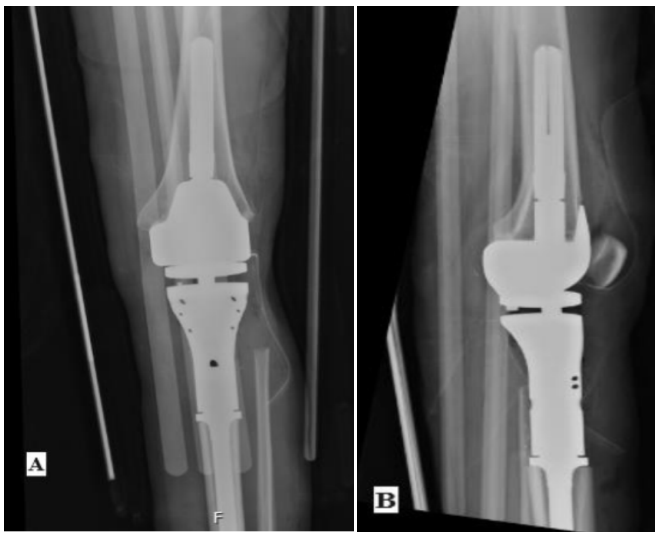

Figure 5: Post-operative X-ray following the radical resection of the left proximal tibia with endoprosthetic reconstruction ([a] coronal view, [b] sagittal view).

Discussion

Malignant GCTB was first described in 1938 by Stewart et al. [5], then Hutter et al. [6] and Dahlin et al. [7] came and differentiated between two types of malignant GCTB, primary and secondary. Primary malignant GCTB is diagnosed when a sarcomatous tissue is seen next to areas of benign GCTB at the initial presentation, whereas secondary malignant GCTB is diagnosed when a sarcoma develops at the site of a previously treated (whether it is surgically or by radiation) benign GCTB.

PMGCTB and SMGCTB both share similar clinical features with benign GCTB [1]. Pain and swelling are usually the most common presenting symptoms [8]. The femur and tibia (especially the distal femur and proximal tibia) are the most common sites of occurrence, as noted in Table 1. In our case, the tumor was in the proximal tibia, and pain was the chief complaint.

Radiologically, malignant GCTB has a similar appearance on imaging to benign GCTB. They mostly present with an epiphyseal osteolytic bone lesion [9], as in our case. There are some other radiologic features that can suggest malignancy, such as invasion of the soft tissues and cortical lysis [8], which were not present in our case.

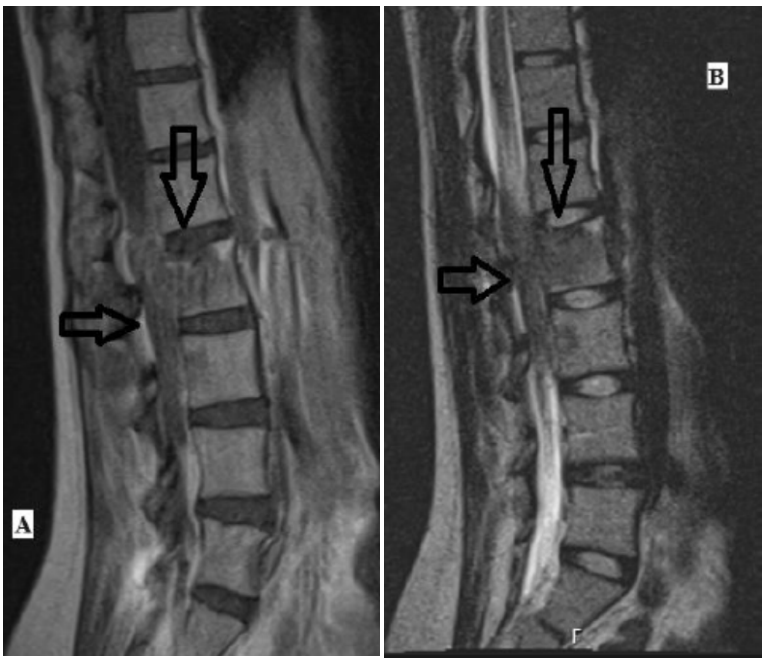

Figure 6: Magnetic resonance imaging of the lumbar spine with and without contrast (20 months following the initial presentation) shows a mass within L2 and L3, in addition to spinal cord enhancement (arrows). (a) (T1 – sagittal view), (b) (T2 – sagittal view).

Histologically, malignant GCTB is considered a high-grade sarcoma [2] with osteosarcoma, fibrosarcoma, and pleomorphic undifferentiated sarcoma being the most common pathologic types [1, 2]. It can be challenging sometimes to differentiate between PMGCTB and giant cell-rich osteosarcoma, even though clinically the management is not different; however, H3 G34W mutation (a specific biomarker for GCTB which was positive in our case) can be useful in confirming the diagnosis of malignant GCTB and ruling out other giant cell-rich tumors of the bone [1].

Metastases have been reported in about 20%–60% of PMGCTB cases. Unfortunately, metastases in malignant GCTB have a worse prognosis compared to the ones in benign GCTB which are usually slow-growing with a better prognosis. Metastases are the leading cause of death in malignant GCTB [10]. In our case, the patient had significant pulmonary and vertebral metastases.

Per the National Comprehensive Cancer Network guidelines [11], we generally follow the same treatment approach when we treat malignant GCTB or osteosarcoma. Therefore, our patient was started on neoadjuvant chemotherapy with MAP regimen upon diagnosis, but unfortunately, she only tolerated one cycle before having the surgery done; then, when she decided to resume chemotherapy, she was started on cisplatin + doxorubicin regimen at USC, which is another first-line therapy for osteosarcoma. Regorafenib is one of the second-line therapies for refractory or metastatic disease.

The medical literature on malignant GCTB is generally scarce. A literature search through PubMed was performed to find the published cases of primary malignant GCTB. Table 1 summarizes all the studies and reported cases of PMGCTB that we have found [2, 8, 10, 12].

Conclusion

Primary malignant GCTB is generally a rare condition, and diagnosis can be difficult due to multiple reasons, including the rarity of the condition, the similar clinical and radiologic presentation of the benign and malignant versions, in addition to the lack of clear diagnostic criteria. Therefore, physicians must always rule out malignancy when they diagnose a GCTB through a thorough histologic examination, as it will drastically change the management and prognosis.

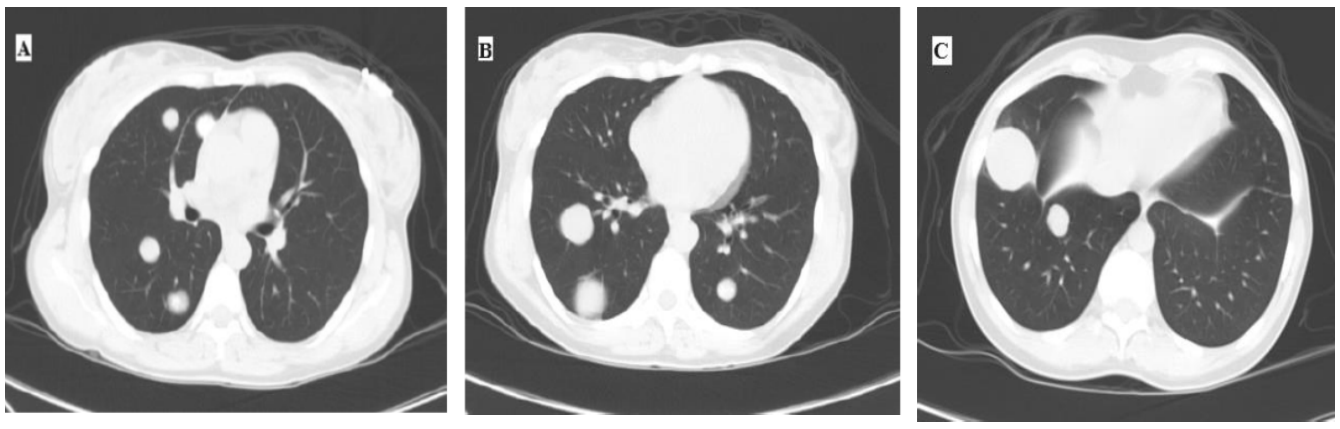

Figure 7: Computed tomography chest without contrast (20 months following the initial presentation) shows multiple metastatic lesions in both lung fields.

Study	Year	Number of cases	Location	Follow up
Hutter et al. [6]	1962	8	Femur – 3	Metastasis – all cases
			Tibia – 1	Death – 5 (mean follow -up period was 18.2 months)
			Patella – 1	
			Illium – 1	
			Humerus – 2	
Dahlin [7]	1970	4	Femur – 3	Death – all cases, 2 from unrelated disease and 2 within 1 year
			Humerus – 1	
Nascimento et al. [13]	1979	8	Femur – 3	Death – 2 (one from metastasis, one from unrelated cause)
			Tibia – 2	No evidence of recurrent disease at the end of the follow -up period (which was 4.5 years) in the remaining 6 patients
			Fibula – 1	
			Scapula – 1	
			Metacarpal – 1	
Dahlin [14]	1985	5	Not reported	Not reported
McDonald et al. [15]	1986	2	Not reported	Mean follow -up period was 7 years, but no specific details were reported about the two cases of PMGCTB
Rock et al. [16]	1986	7	Not reported	Not reported
Anract et al. [8]	1998	17	Distal femur – 6	Death – 10 (longest survival between deaths was 102 months)
			Proximal femur – 1	
			Proximal tibia – 6	
			Sacrum – 2	
			Distal radius – 1	
			Lumbar spine (L5) – 1	
Bertoni et al. [3]	2003	5	Femur – 3	Lung metastases – 2 (one died after 8 months and 1 was alive at 40 months)
			Tibia – 1	No evidence of recurrence in the remaining three cases at 2, 15, and 161 months, respectively
			Ulna – 1	
Domovitov et al. [17]	2009	19	Femur – 8	Death – 4
			Tibia – 11	5-year survival – 87%
			Humerus – 1	
			Radius – 2	
			Fibula – 1	
			Sacrum – 1	
			Illium – 2	
Unni and Inwards [18]	2010	5	N/A	N/A
Chawla et al. [19]	2019	5	Not reported	Not reported
Liu et al. [9]	2020	12	Femur – 5	Metastasis – 6
			Tibia – 6	Death – 5 (all had metastasis)
			Humerus – 1	5-year survival – 56.2%
Palmerini et al. [12]	2021	5	Femur – 2	Death after postsurgical complications from femur replacement – 1
			Pelvis – 1	Chemotherapy with complete response – 1
			Sacrum – 1	Lost to follow -up – 1
			Tibia – 1	Death of primary disease 3 mo after diagnosis of malignancy – 1
				Patient underwent planned amputation plus chemotherapy – 1
PMGCTB: Primary malignant giant cell tumor				

Table 1: Summary of the reported cases of PMGCTB in medical literature.

Clinical Message

The diagnosis and management of primary malignant GCTB are generally difficult, and it is always important to seek an expert opinion from a tertiary cancer center to establish the right diagnosis and treatment plan.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given the consent for his/ her images and other clinical information to be reported in the journal. The patient understands that his/ her names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflict of interest: Nil **Source of support:** None

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