

The Hypermetabolic Giant: 18F-FDG avid Giant Cell Tumor identified on PET-CT


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ABSTRACT

An 87 year-old white female presented with a two-year history of intermittent discomfort in her left foot. PET-CT identified intense 18F-fluorodeoxyglucose (FDG) uptake corresponding to the lesion. Histology of a fine needle aspiration and open biopsy were consistent with a benign giant cell tumor (GCT) of the bone. GCT of bone is an uncommon primary tumor typically presenting as a benign solitary lesion that arises in the end of the long bones. While GCT can occur throughout the axial and appendicular skeleton, it is exceedingly uncommon in the bone of the foot. While 18F-FDG has been established in detecting several malignant bone tumors, benign disease processes may also be identified. The degree of 18F-FDG activity in a benign GCT may be of an intensity that can be mistakenly interpreted as a malignant lesion. Therefore, GCT of the bone can be included in the differential diagnosis of an intensely 18F-FDG-avid neoplasm located within the tarsal bones.

CASE REPORT

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An 87 year-old white female presented to an outside institution with a complaint of intermittent left foot pain for two years. She reported pain after ambulation and occasionally at rest. Her evaluation at the outside institution included radiography, CT, MRI and PET-CT imaging. She was subsequently referred for further evaluation and treatment at our institution. Radiography and CT of the left foot demonstrated a prominent lytic lesion within the lateral aspect of the left cuneiform. The lesion was well demarcated and sclerosis is noted along the proximal and lateral borders in the absence of a periosteal reaction. The anterior surface of the lateral cuneiform was completely resorbed (Figure 1A and 1B). The lesion extended to the articular surface of the lateral cuneiform adjacent to the middle cuneiform (Figure 1B). No calcification was identified within the lesion (Figure 1B).

An 18F-FDG PET-CT scan was obtained using a dose of 16.6 mCi. Imaging of the whole body commenced 62 minutes after injection of radionuclide, and imaging of the lower extremities commenced 88 minutes after dosing. This PET-CT scan demonstrated 18F-FDG avid activity around the periphery of the lesion to a maximal standardized uptake value (SUV) of 10.2 (Figure 1C). No other sites of abnormal uptake were identified to suggest a primary malignant site or other metastatic disease. The maximum intensity projection (MIP) image showed focally increased 18F-FDG uptake in the lateral aspect of the left foot (Figure 1D). For reference, the maximal SUV of the blood pool as measured in the aortic arch was 2.8. The mean SUV of the liver was found to be 2.8. On MRI, T1 weighted coronal image (Figure 2A) and a fat-suppressed T1 weighted coronal image after the intravenous administration of gadolinium contrast (Figure 2B) show a destructive, intensely

enhancing lesion in the lateral cuneiform extending through the dorsal cuneiform into the soft tissues. A fat-suppressed sagittal T2 weighted image (Figure 2C) and a fat-suppressed, gadolinium enhanced sagittal T1 weighted image (Figure 2D) again show the lateral cuneiform lesion and its extension into the dorsal soft tissues.

Fine needle aspiration of the lesion was performed. Analysis of the aspirate smear revealed giant cells and few fragments of spindle cells within a metachromatic matrix. The core biopsy showed fragments of bone, fibrous tissue and few giant cells adjacent to amorphous eosinophilic material, possibly necrotic bone. The findings were nonspecific but were not suggestive of malignancy based on small sampling size. A larger tissue sample was obtained at open biopsy that revealed benign spindle cells with a proliferation of giant cells and hemosiderin-laden macrophages suggestive of a giant cell tumor (see Figure 3). The lesion was curetted during the open biopsy and the resulting osseous defect was grafted.

DISCUSSION

Giant cell tumor (GCT) of the bone, first described by Sir Astley Cooper in 1818 [1], was first distinguished from other bone tumors in 1940 [2]. Giant cell tumor of bone can be identified on radiographic imaging when patients present with pain, swelling, joint movement limitation in the adjacent articulation in the ends of the long bones [3]. Lesions most commonly occur in the proximal tibia, distal femur and radius and less frequently in the vertebrae, pelvis, sacrum, craniofacial bones and skull and skull; it has rarely been reported in the foot (Table 1) [3-15]. Neurologic symptoms can be present when the axial skeleton, particularly the spine, is affected, [16]. Thinning of the bone cortex in weight-bearing regions resulting in pathologic fractures occurs in 10-35% of patients [10, 17, 18]. Giant cell tumors are generally solitary with less than 1% of reported cases being multi-centric (summarized in Table 2) [19].

Approximately 80% of patients with GCT of bone are 20-50 years of age, with the peak prevalence in the third decade of life [10, 20-24]. Similarly, solitary benign GCT affects women more commonly, with ratios from 1.1:1 to 1.5:1 [25]. An even higher female predilection has been found in younger patients and those found in the spine (2.3-2.5:1 ratio) [25-27]. However, publications have reported male predominance as well-one study of 470 cases determined that in patients 21-30 years of age, there is a slight male predominance (1.3:1) [25]. Similarly, malignant GCT has also been reported more common in men (3:1 ratio)[25]. So while a female predominance may be found overall, specific subsets of GCT, ages 21-30 or with malignant disease, may have a male predominance. Radiographically, most GCTs present as a well-defined lytic lesion, extending to the subchondral bone surface in a skeletally mature patient. As with other primary osseous lesions, computed tomography, magnetic resonance imaging and bone scintigraphy are utilized for further characterization and staging. This case report illustrates the characteristic radiologic and histologic appearance of a GCT

within the left lateral cuneiform and emphasizes the avidity of this benign lesion on 18F-FDG PET-CT.

GCT of bone represents 3-5% of all primary bone tumors and accounts for up to 20 percent of all benign bone tumors [28, 29]. GCT typically occurs after skeletal maturity in patients between 20 and 40 years of age, with a peak incidence in the fourth decade (age 32) [28, 30, 31]. GCT of bone occurs much less commonly in pediatric patients. In skeletally immature patients, giant cell tumors commonly arise in the metaphyseal and juxta-epiphyseal region of the long bones with the majority of lesions located eccentrically [32, 33]. The tibia is the most commonly affected site involved in skeletally immature patients [33]. In the metacarpals, radius and fibula, the lesions have been reported to be predominantly centrally located with the bone [32]. Picci, et al. have reported that giant cell tumor in skeletally immature patients occurs in 1.8% of all GCT patients with a predominance of metaphyseal involvement and extension into the epiphysis, suggesting a metaphyseal origin of giant cell tumor in hormonally immature patients [33]. However, the exact site of origin of GCT of bone is debated in the literature. GCT involves the metaphysis, but not the epiphysis, in skeletally immature patients because the open epiphyseal plate acts as a barrier to tumor growth [34]. Multifocal primary GCT is rare and accounts for less than 1% of all GCT [35-38]. Although multicentric GCT is a variant of solitary GCT, its etiology is not known. The age range of patients with multicentric GCT seems to be somewhat younger than the average age of patients with solitary GCT [16]. The knee is the most common site of occurrence in patients with multicentric GCT. There is, however, a reported increased prevalence of involvement in the bones of the hand and feet in patients with multicentric GCT [39]. Patients with poly-articular Paget disease have an increased incidence of multicentric GCT, with 80% of cases being multi-centric (N=5) [40, 41].

GCT involving the bones of the hand and feet is uncommon. 1-5% of GCT cases are reported in the hand and wrist; 1-2% of cases are reported in the foot [4, 12, 42, 43]. The most commonly affected bones in the foot are the head and neck of the talus, followed by the calcaneal tuberosity [33, 44]. However, involvement of the metatarsals and phalanges has been reported [4, 45]. It has also been documented that GCT of the hands and feet tend to occur in younger female patients and are more likely than lesions arising in long bones to undergo local recurrence [4, 8].

PET-CT Imaging

Benign GCT of the bone can demonstrate increased FDG avidity on PET-CT imaging. As a glucose analog, 18F-FDG is transported into cells by surface GLUT-1 transporters and then incorporated into the cell where it is phosphorylated by hexokinase and trapped in cells. The use of FDG-PET is valuable in recognizing malignant tumors as they commonly have increased glycolysis compared to normal tissues result from more GLUT transporters and a higher concentration of hexokinase within malignant cells [46]. The two predominant cell types in GCT of bone are the giant cells, made up of giant osteoclast-like and the neoplastic mononuclear cells, both contribute to the enhanced 18F-FDG utilization seen by PET.

The mononuclear-macrophage cells derive their energy predominantly from glucose metabolism [47-49]. Studies have also reported that benign bone lesions with a 18F-FDG >2.0 standardized uptake value (SUV), including GCT of the bone, have histiocytes and giant cells in the monocyte-macrophage lineage which accumulate 18F-FDG as well [47]. Additionally, fibroblast proliferation in response to osteoclast-like giant cells may also contribute to the relatively high accumulation of 18F-FDG seen in GCT [50]. Aoki, et al. reported a high degree of overlap of 18F-FDG PET SUV between benign and malignant tumors. In particular, GCT demonstrated SUV values as high as >2.0, as did chondroblastomas, sarcoidosis, Langerhans cell histiocytosis and nonossifying fibroma [47]. The presence of the predominant neoplastic mononuclear cells, the giant osteoclast-like cells, and the reactive fibroblast proliferation in GCT of bone may explain the high degree of 18F-FDG uptake, which overlaps with malignant tumors such as osteosarcomas [47]. While several older studies have suggested that a 2.5 SUVmax cut-off could differentiate benign from malignant lesions, a number of major shortcomings, including mismanagement of patients have resulted [51]. Since elevated SUV can be found in benign lesions, as in the present case (10.2 SUV of lesion vs. liver pool SUV of 2.8), it is clear that the 2.5 SUV cut-off does not always allow definite diagnosis and can vary with pattern of uptake [52]. For this reason, the SUV of the lesion is better understood when taken in context with the maximal and mean SUV of the patient's blood pool and liver respectively.

Technetium-99m phosphate bone scans

Giant cell tumors have been shown to exhibit increased radiotracer uptake on technetium-99m phosphate bone scans [53, 54]. In one series, 21 patients with giant cell tumors were imaged with technetium-99m methylene diphosphonate [53]. All GCT in this series had increased radiophosphate uptake, generally more intense at the tumor periphery [53]. However, it was noted that radionuclide bone scanning over-estimated the tumor extent and failed to detect soft-tissue extension in nine patients [53]. The mechanism for increased radioactivity has been attributed to increased blood flow and reactive bone formation at the periphery of the bone [54]; radiotracer activity beyond the actual border of the tumor margin may also be related to reactive bone formation circumscribing the periphery of the lesion [54]. The variability in intensity and pattern of uptake on bone scintigraphic studies may be related to the size of the lesion and other factors including vascularity of the tumor, aneurysmal bone cyst formation, pathologic fracture and tumor necrosis [53]. A diffuse homogenous pattern of radiotracer uptake, as well as a peripherally increased pattern, has been observed. Although bone scanning cannot differentiate benign from malignant tumors based on the intensity of uptake, it may provide visualization of additional sites of uptake in cases of multicentric giant cell tumor and skip lesions [53, 54].

Radiography/CT

Although GCT of bone may cause extensive cortical and cancellous destruction of the cortex as well as expansile remodeling of bone, sclerosis and periosteal new bone formation are not commonly visualized in the absence of a

pathologic fracture [43, 55]. Giant cell tumors typically do not produce matrix calcification on radiography or CT. Some lesions may exhibit a pseudotrabeclated appearance. The pseudotrabeclations may appear as a fine to coarse honeycomb pattern [43]. The lines are formed by alternation between cortical thinning and cortical ridges formed by intracortical pockets of giant cell tumor, but this appearance is not specific for GCT [43]. Lesions typically demonstrate a narrow zone of transition; however in cases of aggressive growth, a wide zone of transition can be seen in approximately 10-20% of cases [12, 42, 43, 55].

CT evaluation of GCT of bone can provide detailed information of the extent of tumor as well as potential soft tissue and articular surface involvement. Additionally, the expanded and thinned cortex and the presence or absence of matrix calcification can be assessed. In cases of intralesional hemorrhage, CT imaging can demonstrate fluid filled levels within the tumor [56]. MRI can provide similar information as the CT scan and is useful in assessing the extent of subchondral extension. Typically, MRI identifies a hypervascular mass with cystic changes [16, 57]. On T1-weighted sequences, the lesions are of low to intermediate signal intensity and are of heterogeneous high signal intensity on T2-weighted images and isointense to adjacent muscle [16, 57]. Low intensity areas in both T1 and T2 weighted images may reflect the large amounts of hemosiderin present following hemorrhage [58, 59]. Fluid levels visualized in some GCTs represent secondary sedentary aneurysmal bone cyst formation [55].

While historically regarded as a benign tumor, giant cell tumors represent a continuum of disease. Grossly, GCT of bone is a fleshy red tumor with both hemorrhagic and cystic areas [59]. If the tumor extends beyond the cortex into the soft tissues, little, if any, periosteal reaction occurs [59]. Typically, the histology includes uniform large osteoclast-type giant cells interspersed with sheets of mononuclear cells, which may be polygonal or elongated [59]. The giant cells may be very large and contain as many as 100 nuclei [59]. While the giant cells are key mediators of the GCT disease process, they are not considered the neoplastic cells in this lesion. The neoplastic component is actually the mononuclear cells that arise from primitive mesenchymal stromal cells, which exhibit a pro-osteoblastic phenotype [59-61]. The neoplastic mononuclear cells express alkaline phosphatase, osteocalcin, matrix metalloproteinases (MMPs), M-CSF, and RANKL (Receptor Activator of Nuclear Factor Kappa-B Ligand), which drives the formation and stimulation of the osteoclast precursors locally [62, 63]. RANKL is a cytokine belonging to the TNF family and is responsible for the formation of giant cells and subsequent bone resorption by these cells [64, 65].

The differential diagnosis of a lytic lesion with multinucleated giant cells is broad and may include aneurysmal bone cyst (ABC), giant cell reparative granuloma, brown tumor of hyperparathyroidism, osteosarcoma with giant cells, and nonossifying fibroma (Table 3) [16, 39, 55]. ABC differs from GCT by its more prominent expansive remodeling, pseudo-trabeclations and fluid-fluid levels on MRI [66]. Secondary ABC is challenging as it may arise in

the presence of GCT, requiring clinical, radiologic, and pathologic correlation of all submitted tissue. Giant cell reparative granuloma occurs in the small bones of the hands and feet, mandible and maxilla; the giant cells cluster around hemorrhage sites [66]. The brown tumor of hyperparathyroidism occurs in the presence of increased parathyroid hormone and abnormal calcium and phosphorous levels [66]. Differentiating osteosarcoma from GCT is generally straightforward; however, when they are purely osteolytic, they can mimic giant cell tumors. Histologically, however, osteosarcoma is made up of osteoblastic spindle cells, which are distinct from the histology of GCT [43, 67]. Occasionally, however, a large number of osteoclasts within an osteosarcoma may suggest a GCT. Similarly, a nonossifying fibroma has a distinct histology with spindle cells arranged in storiform patterns, whorls of connective tissues and interspersed multi-nucleated giant cells and foam cells (lipid-laden macrophages). An increase in the incidence of GCT of bone occurs in patients with other bone diseases, including Paget disease and a sporadic syndrome resembling Noonan disease. GCT developing in Paget disease of bone typically involves the pelvic bones or skull [68]. Unlike the typical anatomic sites noted in primary GCT, giant cell tumors associated with Paget disease are located in the anatomic distribution of the Paget disease and occur in older patients with a long standing history of Paget disease [68, 69]. Giant cell tumors are most commonly identified in the polyostotic form of Paget disease [68, 69]. GCT in Paget disease typically occurs in the skull, facial bones, spine and pelvis [68]. Involvement of the long tubular bones of the extremities is uncommon [68]. Familial clustering of GCT of bone and Paget disease has been reported [70, 71].

GCT is typically a benign lesion; however, its inherent biologic behavior is both variable and unpredictable. Spontaneous malignant transformation of a benign GCT can occur but is extremely rare and is more common following radiation [72, 73]. The time period for malignant transformation is varied, ranging from <1-20 years following radiation therapy [11, 74]. In some cases, recurrence of GCT can occur solely in the soft tissue, possibly from seeding of tumor at the time of excision [75, 76]. Although conventional GCT does not produce sclerosis, recurrence in soft tissue or metastasis to the lungs may produce a shell of calcification along the periphery of the implant, producing a distinct radiographic appearance. Lung metastases do not carry the same severe connotation as they do in other cancers [77, 78]. For this reason, when GCT metastasizes to the lung they are called "benign pulmonary implants" [31, 59]. A true spontaneous malignant transformation occurs in less than 1% of giant cell tumors [79]. The World Health Organization (WHO) designates this as a high-grade sarcoma arising from GCT or at the site of a previous GCT [79]. When this malignant transformation occurs, the prognosis is worse than that of the non-malignant GCT [80]. The 5-year survival of malignant GCT of bone has been reported to be 87% (N=25) compared to 100% in benign GCT (N=244) [81]. Other studies have reported lower 5-year survivals between 0 and 50%; however, these results are likely due to their limited study design including the very few patients investigated [82]. While malignant transformation does decrease survival

compared to non-malignant GCT, the 5-year survival rate of 87% comparable to that found in high-grade spindle cell sarcoma [79].

While the standard options for GCT include curettage, extended curettage or en block excision, the treatment depends on the aggressiveness of the tumor, its location, and the patient's clinical presentation. In the current case, curettage and grafting of the left lateral cuneiform lesion was performed. Recurrences of GCT generally occur during the initial two years, although later recurrences have been reported, necessitating surveillance for at least this long [83].

Giant cell tumor of bone is an uncommon primary bone tumor that typically presents in skeletally mature adults as a benign solitary lesion arising in the end of the long bones. It can occur throughout the axial and appendicular skeleton but is unusual in the hands and feet. Multi-modality imaging, including 18F-FDG uptake on PET scan has been established in detecting malignant bone tumors, but its specificity is not 100%. This case demonstrates the degree of 18F-FDG activity accumulation in a benign giant cell tumor may be of an intensity that can be mistaken for a malignant lesion. Giant cell tumors can be included in the differential diagnosis of intensely 18F-FDG-avid neoplasms located within the tarsal bones.

TEACHING POINT

The degree of 18F-fluorodeoxyglucose activity by PET in benign giant cell tumor may be of a high enough intensity that it can be mistakenly interpreted as a malignant lesion. Giant cell tumors, in addition to several other benign bone processes, should be included in the differential diagnosis of an intensely 18F-fluorodeoxyglucose-avid neoplasm located in the tarsal bones.

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FIGURES

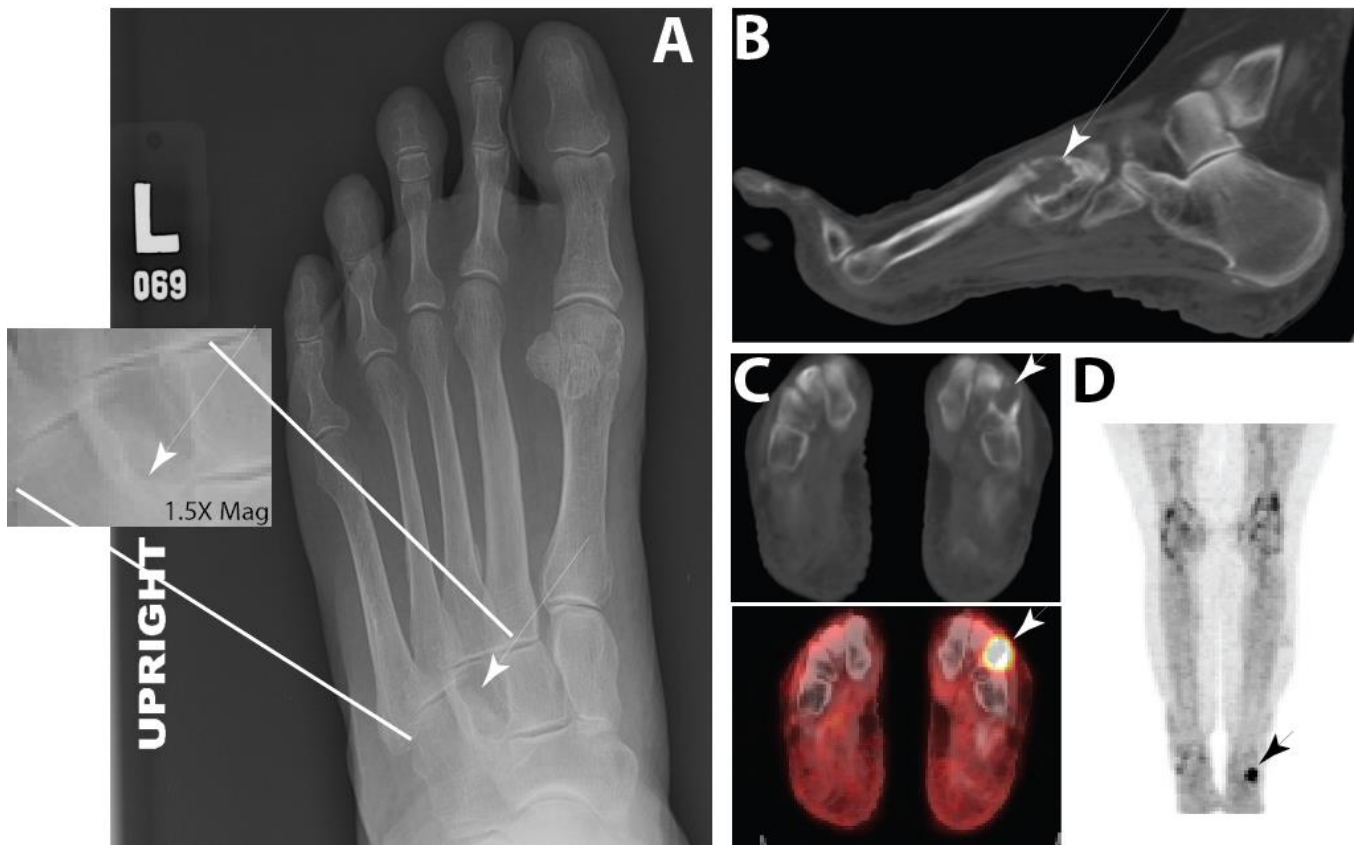


Figure 1: Radiographic, CT, and PET imaging studies of giant cell tumor of the bone in an 87 year-old white female presenting with intermittent left foot pain. A. Antero-posterior radiographic view of the left foot demonstrates a large well-circumscribed lytic lesion in the lateral cuneiform (white arrow). The margins of the lesion are well defined. Sclerosis is noted along the proximal and lateral borders of the lesion B. A sagittal CT reconstruction of the foot depicts an extensive lytic lesion with mildly sclerotic borders at the inferior and proximal margins of the lesion (white arrow). C. Axial CT image of the foot shows the lytic lesion (white arrows) in the left lateral cuneiform (top image) with an associated localized 18F-FDG uptake on the fused PET-CT axial image (bottom image). 16.6 mCi of F-18-FDG was administered. The time of imaging of the whole body commenced at 62 minutes after F-FDG was administered, however the imaging of the lower extremities specifically occurred 88 minutes after dosing. D. The maximum intensity projection (MIP) image of the lower extremities shows increased metabolic activity (intense FDG uptake) within the lateral aspect of the left foot. The maximal lesion SUV was found to be 10.2; the maximal SUV of the aortic arch blood pool was 2.8. The mean SUV of the liver was found to be 2.8. Sagittal CT images were taken using a GE LightSpeed 16 with 5x5 mAs and a kVp of 70, without IV contrast; PET/CT images were collected using a GE Discovery ST.

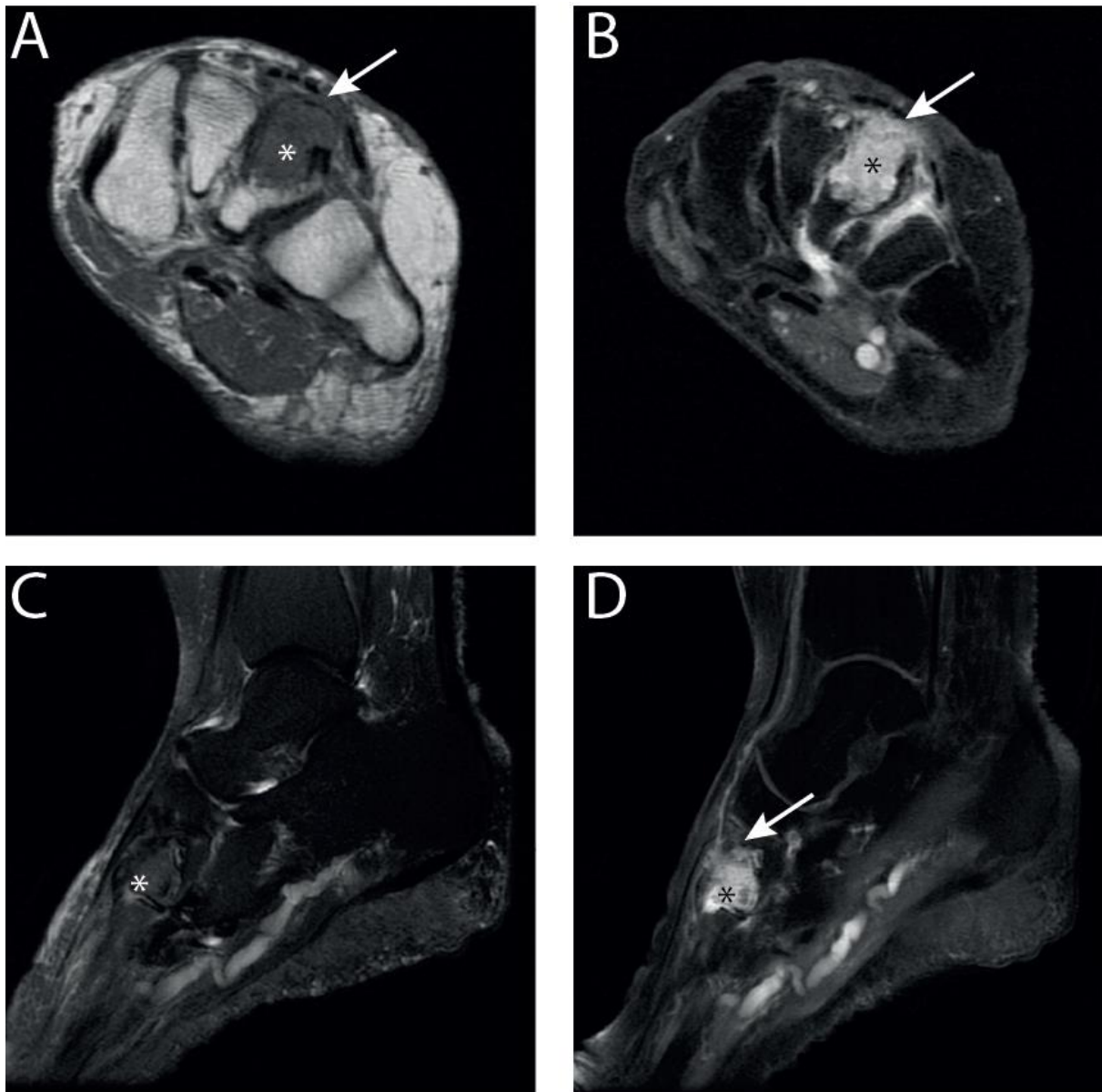


Figure 2: MRI of giant cell tumor of the bone in an 87 year-old white female with Giant cell tumor of the left lateral cuneiform bone presenting with intermittent left foot pain. A. T1 weighted coronal image shows a destructive lesion in the lateral cuneiform extending into the dorsal soft tissues deep to the extensor tendons. B. Gadolinium-enhanced, fat-suppressed T1 weighted coronal image demonstrates intense enhancement of the lesion and enhancement surrounding tissue about the remainder of the lateral cuneiform. C. Fat-suppressed T2 weighted sagittal image again shows the lateral cuneiform lesion. D. Fat-suppressed, gadolinium-enhanced T1 weighted sagittal image demonstrates the lesional enhancement and the soft tissue extent of the tumor deep to the extensor tendons dorsally. MR images were collected using a GE Tesla, Hitachi 1.2 open scanner. The contrast material used was Magnevist at 14cc's. *=lesion in the lateral cuneiform. Arrow=soft tissue extension of the tumor.

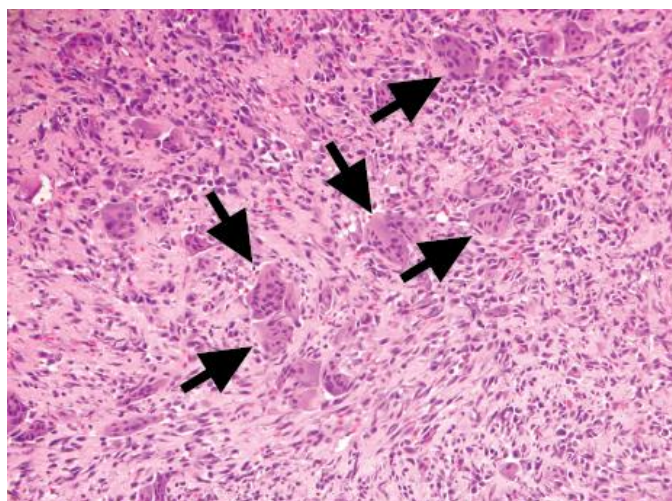


Figure 3 (left): Histological section of a bone fragments collected from a resection taken from an 87 year-old white female with Giant cell tumor of the left lateral cuneiform bone. Histological analysis reveals a variably cellular neoplastic process characterized by scattered round to oval polygonal mononuclear cells with admixed numerous osteoclast-like multinucleated giant cells (see arrows). The nuclei within the mononuclear and multinucleated cells have a similar appearance with open chromatin and small inconspicuous nucleoli. Some of the mononuclear cells have a spindled appearance. Scattered but infrequent mitotic figures are present. The background stroma is variably collagenized and fibrotic. Foci of hemosiderin deposition are present. The tumor is expansile and disrupts adjacent bone. Hematoxylin and Eosin stained image captured at 100X magnification.

Frequently occurs	Rarely occurs
Proximal tibia	Foot
Distal femur	Hand
Distal Radius	Vertebral bodies
Sacrum	Sternum
Distal tibia	Ribs
	Skull

Table 1: Distribution of Giant Cell Tumor of bone

Etiology	<ul style="list-style-type: none"> Exact origin is not known Ultrastructural analysis suggests the “stromal” cell, or mononuclear spindle cell, is neoplastic Osteoclastic giant cells and mononuclear rounded cells are reactive
Incidence	<ul style="list-style-type: none"> GCT of bone ~3-5% of all primary bone tumors; up to 20% of all benign bone tumors Of all GCT of bone, hand and foot incidence low (1.7% and 1.2%, respectively)
Gender ratio	<ul style="list-style-type: none"> Slight male predominance in general GCT of hand and foot bones: Slight female predominance
Age predilection	<ul style="list-style-type: none"> Typically occurs after skeletal maturity Patients 20-40 years of age Peak incidence around age 32 Uncommon in pediatric patients
Risk factors	<ul style="list-style-type: none"> Associated with Paget Disease (rarely)
Treatment	<ul style="list-style-type: none"> Curettage to en block excision Dependent on location, presentation, and aggressiveness of the tumor
Prognosis	<ul style="list-style-type: none"> GCT of the bone is typically a benign lesion; biologic behavior is variable and unpredictable Spontaneous malignant transformation can occur, but extremely rare and more common following radiation Lung seeding “benign pulmonary implants” may occur Only a small number of cases of true spontaneous malignant transformation reported Prognosis better than other high-grade sarcomas (50% five year survival)
Findings on imaging	<p><i>Plain film and CT:</i></p> <ul style="list-style-type: none"> Typically presents as a solitary lesion arising in the end of the long bones by x-ray. Narrow transition zone (broader transition zone seen in more aggressive GCTs) Most do not have surrounding sclerosis (80-85%) <p><i>MRI:</i></p> <ul style="list-style-type: none"> T1-low to intermediate solid component. Low signal periphery. Solid components enhance, and some enhancement may be seen in adjacent bone. T2-heterogeneous intermediate to high signal (variable). Low signal periphery. <p><i>Scintigraphy/bone scan:</i></p> <ul style="list-style-type: none"> Increased uptake on delayed images, with a central photopenic region (doughnut sign) Increased blood pool activity is seen due to regional hyperemia. <p><i>PET:</i></p> <ul style="list-style-type: none"> GCTs intensely ¹⁸F-FDG-avid benign neoplasms found in bones throughout the body.

Table 2: Summary table of giant cell tumor (GCT) of bone

Disease	Description	Histology	Radiograph	MRI	CT
Aneurysmal bone cyst	<ul style="list-style-type: none"> May arise or be associated with other tumors (including giant cell tumor) 	<ul style="list-style-type: none"> Blood-filled spaces without endothelial lining Numerous benign giant cells Strands of bone present in fibrous tissue of septa. 	<ul style="list-style-type: none"> Radiographically expansive, eccentric, and lytic lesions with bony septae are present Appears bubbly 	<ul style="list-style-type: none"> MRI or CT scan will identify multiple fluid lines. 	
Giant cell reparative granuloma	<ul style="list-style-type: none"> Reactive process that occurs in the small bones of the hands and feet, mandible and maxilla. 	<ul style="list-style-type: none"> Giant cells cluster around hemorrhage sites. 	<ul style="list-style-type: none"> Lytic and expansile, but extension to the epiphysis is not common Not usually as aggressive as GCT on radiographs [16, 84] Indistinguishable from other lesion types by radiograph 	<ul style="list-style-type: none"> Expansile and lytic lesions hypointense T1- and T2-weighted images with homogeneous contrast enhancement Non-specific findings [85] 	
Brown tumor of hyperparathyroidism	<ul style="list-style-type: none"> Present in a patient with increased parathyroid hormone and abnormal calcium and phosphorous levels. 	<ul style="list-style-type: none"> Areas of bone resorption-replacing fibroblastic tissue contains osteoclast-like giant cells GCT lacks fibrogenic stroma found in BT or hyperparathyroidism 	<ul style="list-style-type: none"> Expansile and well marginated and may mimic GCT when in the small bones of the hand Radiographic features of hyperparathyroidism, specifically subperiosteal resorption [84] 	<ul style="list-style-type: none"> Iso-intensity to gray matter on T1-weighted images Heterogeneous hyperintensity on T2-weighted images, intense enhancement [86] 	<ul style="list-style-type: none"> Expansile soft-tissue attenuation mass; expansile Lytic changes in surrounding bone [86]
Osteosarcoma with giant cells	<ul style="list-style-type: none"> Primary bone tumor with presence of osteoid (bone formation) within the tumor. At times, they may exhibit multinucleated osteoclast-like giant cells. 	<ul style="list-style-type: none"> Differentiated easily by histology When osteosarcoma is purely osteolytic, can mimic giant cell tumors Osteosarcoma is made up of osteoblastic spindle cells, distinct from the histology of GCT 	<ul style="list-style-type: none"> X-ray is diagnostic "Codman's triangle", subperiosteal lesion formed with periosteum is raised secondary to the tumor, is suggestive Biopsy only definitive diagnosis Osteosarcoma (with giant cells) can be radiographically indistinguishable from GCT [84] 	<ul style="list-style-type: none"> Non-specific findings: On T1-weighted images, homogeneous low signaling intensity. On T2-weighted images, high signal intensity mixed with low [87] 	<ul style="list-style-type: none"> Non-specific findings Cortex thinning, ballooning lesion without destruction [87]
Nonossifying fibroma	<ul style="list-style-type: none"> Foci consisting of collagen rich connective tissue in bone rich in fibroblasts, histiocytes, and osteoclasts. Benign lesion found commonly in children incidentally. 	<ul style="list-style-type: none"> Nonossifying fibroma has a distinct histology with spindle cells arranged in storiform patterns Whorls of connective tissues, and interspersed multinucleated giants cells and foam cells (lipid-laden macrophages). 	<ul style="list-style-type: none"> Generally, sharply demarcated, asymmetrical, cortically based lucencies with a thick sclerotic rim (usually multi-loculated). No periosteal reaction, no "Codman Triangle", no cortical breach and no associated soft tissue mass 	<ul style="list-style-type: none"> If CT or MRI is obtained for nonossifying fibroma, the cortex will appear interrupted and may be interpreted as cortical destruction [84] 	
Giant cell tumor of bone	<ul style="list-style-type: none"> Heterogeneous bone tumor composed of giant-cell tumor stromal cells (neoplastic, of osteoblastic origin), intermixed with mononuclear histiocytic cells and multinucleated giant cell fractions, which are non-neoplastic. 	<ul style="list-style-type: none"> Typically, the histology includes uniform large osteoclast-type giant cells interspersed with sheets of mononuclear cells (polygonal or elongated). GCT are not considered the neoplastic cells in this lesion Mononuclear cells that arise from primitive mesenchymal stromal cells, exhibit a pro-osteoblastic phenotype 	<ul style="list-style-type: none"> Radiolucent lesion having sharp but non-sclerotic margin [88] 	<ul style="list-style-type: none"> CT or MRI may reveal fluid levels representing layering of blood [88] 	

Table 3: Differential diagnosis table of giant cell tumor of the bone

ABBREVIATIONS

ABC = Aneurysmal bone cyst
CT = Computed Tomography
FDG = Fluorodeoxyglucose
GCT = Giant cell tumor
MRI = Magnetic Resonance Imaging
PET = Positron Emission Tomography
SUV = Standard uptake value

KEYWORDS

giant cell tumor of bone; lateral cuneiform; 18F-FDG, PET-CT

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