

# Transformation of Benign Giant Cell Tumor of Bone Into Epithelioid Angiosarcoma

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## Abstract

In this article, we report a case of transformation of a benign giant cell tumor (GCT) of the calcaneus into an epithelioid angiosarcoma. The patient presented to our service in 2003 and was followed until 2014. Transformation occurred 11 years after curettage, cryotherapy, cementation, and a well-documented disease-free interval. Longitudinal radiographs, magnetic resonance imaging, and histopathology were evaluated by the same medical team.

There are only a few case reports and case series of malignancy associated with GCT of bone. To our knowledge, this case report is the first to describe an assessment of the transformation of a benign GCT of bone into an epithelioid angiosarcoma. Orthopedic surgeons, radiologists, oncologists, and pathologists should be aware of the potential for transformation of benign GCTs to high-grade sarcomas after a long disease-free interval.

**G**iant cell tumors (GCTs) of bone account for about 5% of all primary bone tumors in adults, with a predominance in the third decade in life.<sup>1</sup> Clinically, GCT of bone often presents with pain, pathologic fracture, and/or soft-tissue expansion in the epiphysis of long bones. However, GCT of bone also has been reported in non-long bones, such as the talus and the calcaneus.<sup>2,3</sup> Histologically, GCT of bone consists of neoplastic stromal cells, mononuclear histiocytic cells, and multinucleated giant cells that resemble osteoclasts.<sup>4</sup> The radiologic appearance of GCT is often described as a lytic, eccentrically located bony lesion that extends near the articular surface

in patients with closed physes. Many GCTs have aggressive radiologic features with possible extensive bony destruction and soft-tissue extension.

Although categorized as a benign lesion, GCT can be locally aggressive, with a variable local recurrence rate of 0% to 65%, depending on treatment modality and skeletal location. Given the aggressiveness of GCT of bone, recommendations for operative intervention include intralesional curettage with adjuvant therapy (eg, cryotherapy, phenol, argon beam, electrocautery) and placement of bone void fillers (eg, bone graft polymethylmethacrylate). Wide resection is recommended when the articular surface is no longer viable for reconstruction secondary to extensive destruction. Some authors have reported that surgical margin is the only risk factor in local recurrence,<sup>5,6</sup> and thus complete resection may be needed for tumor eradication. In addition, about 3% of GCTs demonstrate benign pulmonary implants, which have been cited as cause of death in 16% to 25% of reported cases of pulmonary spread.<sup>7,8</sup>

The literature includes few reports of primary or secondary malignant transformation of GCT. Hutter and colleagues<sup>9</sup> defined primary malignant GCT as GCT with sarcomatous tissue juxtaposed with zones of typical benign GCT cells. Secondary malignant GCT is a sarcomatous lesion at the site of a previously documented benign GCT. Secondary malignant GCT of bone histologically has been classified as a fibrosarcoma, malignant fibrous histiocytoma, or osteosarcoma transformation.<sup>10</sup>

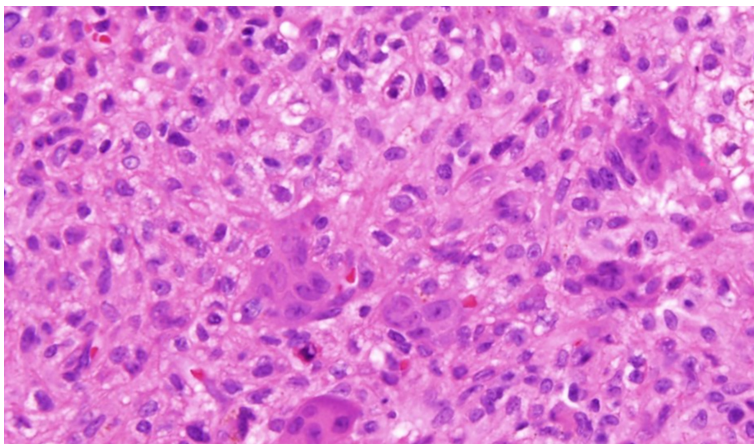
## Take-Home Points

- Malignant transformation of a benign GCT is extremely rare.
- It is difficult to distinguish between an early malignant transformation and an overlooked malignancy.
- The most common clinical presentation of transformation of GCT into malignancy is pain, often with swelling.
- Interval monitoring of GCTs may be necessary in patients with symptoms concerning for malignant transformation.
- Clinicians should maintain a high clinical suspicion for malignant transformation or late recurrence of GCT in a patient with new pain at the wound site.

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**Figure 1.** Plain radiographs before surgery in July 2003 (A, lateral; B, oblique), (C) 2 weeks after surgery, and (D) 6 weeks after surgery show interval curettage, cryotherapy, and cementation of a giant cell tumor of the calcaneus.



**Figure 2.** Giant cell tumor. Several multinucleated osteoclastic giant cells are scattered among many cytologically bland mononuclear cells (hematoxylin-eosin, original magnification  $\times 40$ ).

Most malignant transformations of GCT of bone have been attributed to previous irradiation of the lesion.<sup>11,12</sup> However, there are some case reports of benign bone GCT malignant transformation in situ without any other medical intervention. It was reported that non-radiation-induced secondary transformations occur relatively early after GCT treatment.<sup>13</sup> During the early stages of tumor recurrence, however, it is difficult to distinguish between malignant transformation and primary disease overlooked as a result of sampling error.

We report a case of secondary malignant transformation of GCT of bone 11 years after surgical curettage, cryotherapy, and cementation without adjuvant radiation therapy. To our knowledge, this

case report is the first to describe transformation of a nonirradiated benign GCT into an aggressive, high-grade epithelioid angiosarcoma, a very rare vascular bone tumor. The patient provided written informed consent for print and electronic publication of this case report.

## Case Report

In July 2003, a 46-year-old woman presented with left heel pain of several months' duration. Plain radiographs showed a nonaggressive-appearing lytic lesion of the superior aspect of the posterior calcaneal tuberosity with a small cortical incongruity along the superior margin of the lesion (**Figures 1A-1D**). A biopsy specimen of the calcaneal lesion showed a classic GCT of bone with exuberant fibroxanthomatous inflammatory infiltrate. Multinucleated osteoclasts had no malignant features. There was no necrosis or atypical cells. Immunohistochemical staining was positive for CD68 in giant cells and negative for human epidermal growth factor receptor 2 (HER2)/neu (**Figure 2**). Definitive surgery included curettage, cryotherapy, and cementation of the GCT of the calcaneus. The GCT was removed with extended curettage and use of a motorized burr. Liquid nitrogen was placed in the curetted area to decrease local recurrence, and cement was placed to fill the defect and restore structural integrity.

A postoperative splint was placed, and weight-bearing progressed over 6 weeks. The patient was followed at 2- to 3-month intervals over the first 5 postoperative years. She was able to work and perform activities of daily living, but her postoperative course was complicated by significant chronic pain in multiple extremities and long-term treatment by the chronic pain service. At no time did postoperative imaging—magnetic resonance imaging (MRI) at 6 years, whole-body bone scan at 7 years, plain radiographs at 10 years—show evidence of recurrence.

Radiographs showed stable postoperative changes with a small radiolucent area (with sclerotic rim) surrounding the cement-bone interface. Given its proximity to the Achilles tendon and more motion than usual at the wound site, the radiolucency likely was caused by small movements of the interface. The radiolucent area remained stable over a 15-month period.

Whole-body bone scan showed a small area of osteoblastic activity in the left calcaneus, consistent with inflammation surrounding the bone-cement interface, but the uptake was minor relative

to other areas of signal, and there were no significant inflammatory reactive changes on MRI (Figures 3A, 3B).

Over 11 years, regular 6- to 12-month follow-up examinations revealed no significant changes in the left foot or in plain radiographs of the chest. In addition, physical examinations revealed no evidence of a palpable mass of the left foot.

In July 2014 (11 years after curettage and cementation), the patient presented to her pain clinic appointment with severe left foot pain. She said that, over a few weeks, she experienced a significant increase in pain and developed posterolateral foot swelling, which limited her ability to ambulate. Plain radiographs showed a significant soft-tissue prominence around the

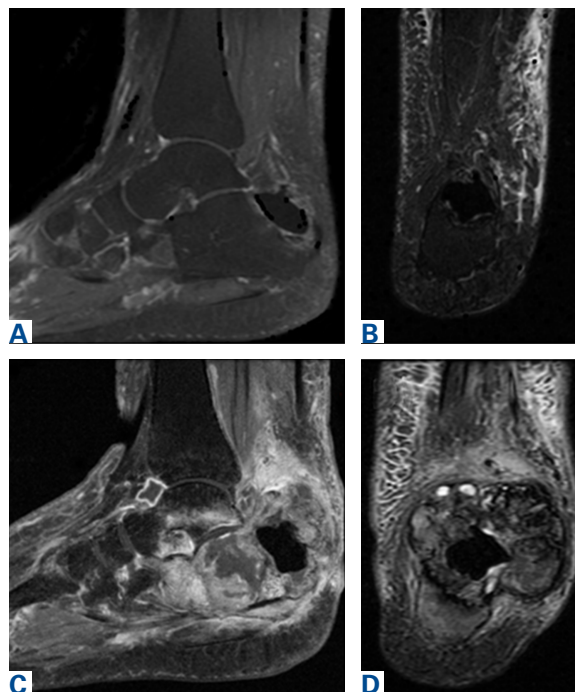
posterior calcaneus, increased lucency around the bone-cement interface in the calcaneus with elevation, and a cortical break of the superior margin of the posterior calcaneus (Figures 3C, 3D). MRI showed a large lobular mass in the calcaneus and surrounding soft tissue with T1 and T2 signal heterogeneity and enhancement after administration of gadolinium (Figures 4A-4D). There was a large extraosseous extension of the calcaneus-based mass laterally and superiorly with edema in the surrounding hindfoot region (Figure 4).

Physical examination revealed exquisite tenderness along the lateral and posterior aspects of the left hindfoot. The patient was unable to bear weight and had soft-tissue swelling throughout the foot and mid calf as well as a palpable mass in the posterior heel. She was otherwise neurovascularly intact through all distributions of the left lower extremity. It was unclear if the GCT of the calcaneus had recurred or if there was a new, secondary tumor. Given her severe pain and morbidity, the patient decided to proceed with open biopsy and a pathology-pending plan for possible amputation in the near future.

In August 2014, an open biopsy with intraoperative frozen evaluation yielded a diagnosis of malignant neoplasm not otherwise specified. Permanent sections showed a proliferation of malignant epithelioid cells with extensive necrosis, hemorrhage, and hemosiderin deposition but no multinucleated giant cells. Malignant cells were stained with endothelial markers CD31, ERG, and D2-40 and were negative with melanoma markers



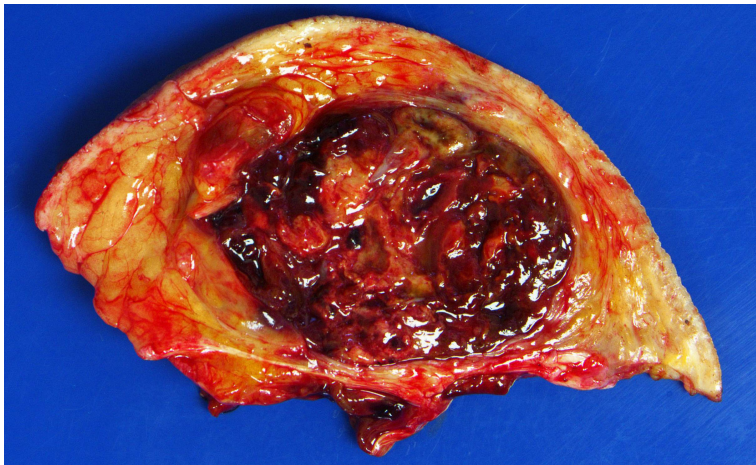
**Figure 3.** (A) Oblique and (B) lateral plain radiographs before de-differentiation (July 2009) and (C) oblique and (D) lateral plain radiographs after de-differentiation with interval development of a soft-tissue mass around the cement (July 2014).



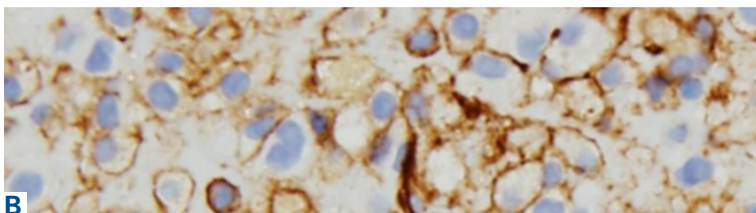
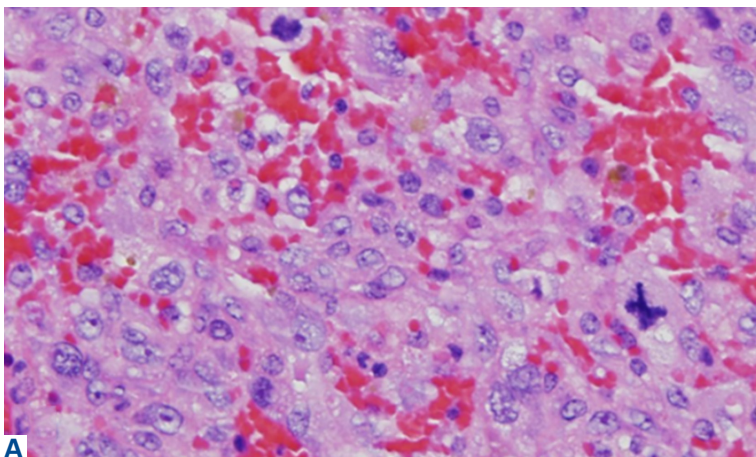
**Figure 4.** (A, B) Magnetic resonance imaging in July 2009 (6 years after surgery; ) and (C, D) July 2014 (11 years after surgery) shows interval development of an expanding aggressive-appearing lesion of the calcaneus encasing the prior cementation, concerning for malignant transformation.

and pan-keratin stains. A diagnosis of high-grade epithelioid angiosarcoma was made with this open biopsy specimen (Figure 5).

Transformation of the GCT into a high-grade epithelioid angiosarcoma prompted presentation of the patient's case to a multidisciplinary board of



**Figure 5.** Gross specimen from definitive below-knee amputation shows large bone and soft-tissue mass with destruction through calcaneal cortex.



**Figure 6.** Epithelioid angiosarcoma. (A) Solid proliferation of malignant epithelioid cells with enlarged vesicular nuclei; X-shaped atypical mitotic figure near the center of the field (hematoxylin-eosin, original magnification  $\times 40$ ). (B) Positive membranous pattern of staining in most malignant cells (CD31, original magnification  $\times 40$ ).

physicians with a focused clinical practice in sarcoma management. The board included board-certified specialists in orthopedic oncology, pathology, musculoskeletal radiology, medical oncology, and radiation oncology. Although discussion included pre-resection use of neoadjuvant chemotherapy to evaluate for disease response, the patient's severe pain led her to forgo this treatment and proceed directly to below-knee amputation.

Amputation revealed a 7.7-cm hemorrhagic ne-

croitic mass composed of a highly cellular spindle and epithelioid malignancy with abundant hemosiderin deposition (Figure 5). In addition, several atypical mitotic figures and malignant multinucleated *tumor* giant cells were randomly scattered throughout the neoplasm. However, there were none of the bland osteoclastic giant cells typical of those found in the curettage specimen 11 years earlier. Multiple sections revealed no evidence of residual GCT of bone (Figures 6A, 6B). The patient's postoperative course was uncomplicated, and she was discharged on postoperative day 4.

At first follow-up, the patient reported significant pain relief and asked to begin titrating off her chronic pain medicine. Clinical staging, which involved performing whole-body positron emission tomography/computed tomography, revealed nothing concerning for metastases. When this report was being written, the patient was being monitored for recurrent disease in accordance with National Comprehensive Cancer Network guidelines. In the absence of residual sarcoma, our medical oncology team discussed adjuvant chemotherapy options with her. Subsequently, however, she proceeded only with observation and periodic imaging.

### Discussion

Malignant transformation of a benign GCT is extremely rare, especially in cases in which the tumor bed has not previously undergone radiation therapy. Although the literature includes historical case reports, primary and secondary malignant GCTs comprise  $<9\%$  of all GCTs.<sup>11,13,14</sup> Primary bone epithelioid angiosarcoma is also extremely rare, especially in the calcaneus; only 1 case is described in the literature.<sup>15</sup> In this article, we report on a benign GCT of bone that transformed into an epithelioid angiosarcoma more than a decade after the GCT was treated with curettage and cementation.

The fact that the malignant areas of a previous tumor may have been missed because of sampling error is important for benign GCT of bone in the early postoperative period, as distinguishing between early malignant transformation and an overlooked malignancy may not be possible. However, transformation is more likely the case when a benign GCT becomes a high-grade malignancy after a long disease-free interval. Several authors have indicated that a benign GCT tumor recurring with a secondary malignancy 2 to 5 years after initial GCT treatment suggests malignant transformation.<sup>16</sup> Grote and colleagues<sup>10</sup> compiled reports

of malignant transformation of GCT of bone and described the clinicopathologic features of secondary malignant transformation of GCTs. The data they compiled and data from several other studies indicate a poor prognosis after malignant transformation of GCT; 4 years after diagnosis, mean survival is 40% to 50%.<sup>10,16</sup> The most common clinical presentation of transformation of GCT into malignancy is pain, often with coincident swelling of the native wound bed. However, a few cases have been identified with radiologic imaging alone and without a period of clinical symptoms.<sup>16</sup>

To our knowledge, this case report is the first to describe a longitudinal assessment of the transformation of a benign GCT of bone into an epithelioid angiosarcoma. Whereas an earlier reported GCT of bone transformed into epithelioid angiosarcoma after irradiation,<sup>12</sup> our patient's GCT of bone transformed without irradiation. GCTs of bone are locally aggressive benign tumors and are relatively rare. Malignant transformation of a benign bone tumor a decade after initial, definitive treatment is concerning, especially given the poor prognosis after malignant transformation in this clinical scenario. Current adjuvant treatments have not changed the prognosis. The literature includes a wide variety of histologic transformations, including high-grade sarcomas, after a long disease-free interval. Although malignant transformation of benign GCTs is rare, clinicians should be aware of the potential. Interval monitoring of GCTs may be necessary in patients with symptoms concerning for malignant transformation—pain or swelling in the wound bed—and patients should know to immediately inform their physician of any changes in pain level or local wound bed. Clinicians should maintain a high clinical suspicion for malignant transformation or late recurrence of GCT in a patient with new pain at the site of a previously treated GCT of bone with a disease-free interval of several years.

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*This paper will be judged for the Resident Writer's Award.*