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CASE REPORT

# Giant cell tumor complicating Paget disease of long bone

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**Abstract** Giant cell tumor (GCT) is a rare complication of Paget disease of bone. It usually occurs in the skull or pelvic bones of patients with long-standing polyostotic disease. This report describes a 62-year-old patient who presented with monostotic Paget disease of the distal femur complicated by GCT. He had a 2-year history of discomfort and pain in his left knee. Conventional plain films and MRI demonstrated the characteristic bone changes of Paget disease and an associated lytic lesion involving the epiphyseal and metaphyseal regions of the distal femur. A diagnostic curettage showed the characteristic histopathologic features of Paget disease and GCT. There was no evidence of malignancy. The clinicopathologic features of this rare lesion are described and correlated with a review of the literature.

**Keywords** Giant cell tumor · Paget disease · Bone tumor

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## Introduction

Paget disease of the skeleton is a well-known disorder of unclear etiology that results in deformity and enlargement of single or multiple bones due to abnormal osteoclastic–osteoblastic remodeling of bone. The disease affects 3% of the population aged over 40 years in the USA and the UK and is very rare in younger patients [1]. More recently, the disease has been on the decline for reasons yet to be fully elucidated. It is common in populations of northern European descent, including those of Australia, Great Britain and the USA, but it is infrequently observed in Scandinavia. It is only rarely seen in populations of the Middle East and Asia. Familial forms of Paget disease have been documented [1].

Major complications of Paget disease include fracture, osteoarthritis, and, very rarely, high-output cardiac failure [2, 3]. The development of a high-grade sarcoma, usually osteosarcoma, occurs in approximately 1% of patients and carries an extremely poor prognosis [4, 5]. Such complications are more often seen in patients with the polyostotic form of the disease. Giant cell tumor (GCT) is a very rare complication of Paget disease that usually occurs in the skull or pelvis and is uncommon in long bones of the extremities [6]. We present a case of Paget disease of the distal femur that initially presents with GCT and compare the clinicopathologic features with those reported in the literature.

## Case presentation

A 62-year-old man presented to the Orthopaedic Clinic with a 1-year history of pain in his left knee. The pain was gradually increasing, and recently he had had difficulty straightening and bending his knee. His past medical history was remarkable for diabetes mellitus and coronary artery disease for which he had undergone coronary bypass surgery. There was no family history of bone disease or tumors. The patient had no known family ties to Avellino, Italy.

Physical examination revealed a healthy appearing man who walked with an antalgic limp. He moved about easily but used a cane. Examination of his left knee revealed a 50° flexion contracture, and he was able to flex his knee to 110°. There was vague soft tissue thickening around the knee, but no appreciable joint effusion. He had bilateral pitting edema and normal sensation and circulation in both lower extremities. Laboratory findings were reported to be within normal limits; however, a serum alkaline phosphatase level was not specified.

Conventional radiography of the left distal femur revealed a lytic lesion with associated coarsening and thickening of the trabeculae, extending from the epiphysis to the distal diaphysis and terminating in an angular flame-shaped configuration. The cortex at the posterior aspect of the metaphysis was thinned and partially destroyed. In addition, there was an ill-defined area of greater radiolucency involving the medial femoral condyle (Fig. 1a,b). On T1-weighted images (WI), MRI demonstrated coarse bone trabeculae and a mass characterized by decreased signal intensity (SI) in the medial femoral condyle (Fig. 2a). On T2-WI the mass in the medial femoral condyle showed increased signal intensity with a more prominently bright SI at the center. T1-WI with contrast showed peripheral enhancement and lack of enhancement at the center of the tumor (Fig. 2b–e). The bright SI on T2 images with a lack of signal enhancement following the administration of contrast agent suggested the presence of fluid in the center of the tumor. A technetium bone scan showed increased uptake in the left distal femur. The radiological findings were those of a lytic tumor, suggestive of a sarcoma superimposed on a background of Paget disease. A diagnostic curettage was performed.

Histological examination of the biopsy material was remarkable for multiple fragments of cortical and cancellous bone. There was medullary fibrosis of the cancellous bone, and the trabeculae were composed of woven and lamellar bone with numerous cement lines. In some areas the cement lines had a mosaic pattern. The cortical bone also showed similar evidence of extensive remodeling. The trabeculae were lined by plump activated appearing osteoblasts and abundant large osteoclasts with vacuolated cytoplasm. The histopathologic findings were typical of Paget disease of bone (Fig. 3). Multiple fragments of a giant cell rich tumor were admixed with the Pagetic bone (Fig. 4a). The tumor was composed of sheets of large multinucleated osteoclast-like giant cells with nuclei ranging from 10 to 30 in number, interspersed with polygonal mononuclear cells with similar appearing nuclei (Fig. 4b). Focally, the mononuclear cells had fibroblastic spindle cell morphology. Intranuclear inclusions were not identified by light microscopy. Secondary aneurysmal bone cyst (ABC) change and peripheral reactive woven bone formation were present as well. There were no areas of increased cellularity, cytological atypia, atypical mitotic figures, bone formation as seen in osteosarcoma, or other features of malignancy. Therefore, a diagnosis of GCT complicating Paget disease was made.

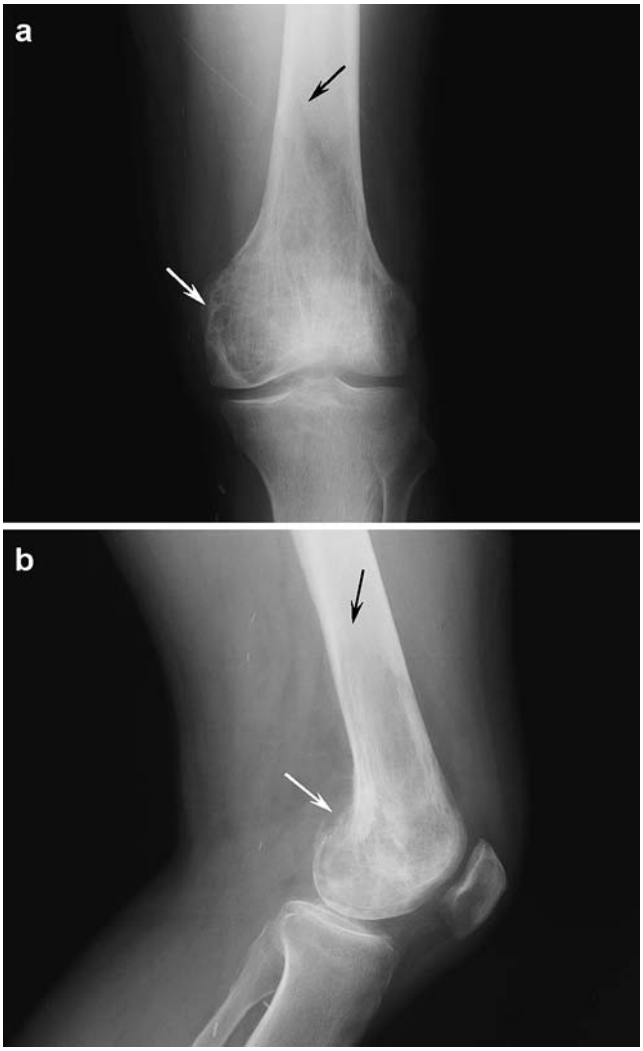


**Fig. 1** Anteroposterior (**a**) and lateral (**b**) views of the right femur, showing coarsely trabeculated rarefaction involving the distal femoral shaft and condyle. Proximally, an advancing wedge-shaped translucent edge is seen at the interface with normal bone (*black arrow*). The medial condyle is remarkable for an area of vague lucency and an indistinct cortex at the posterior aspect of the condyle (*white arrow*)

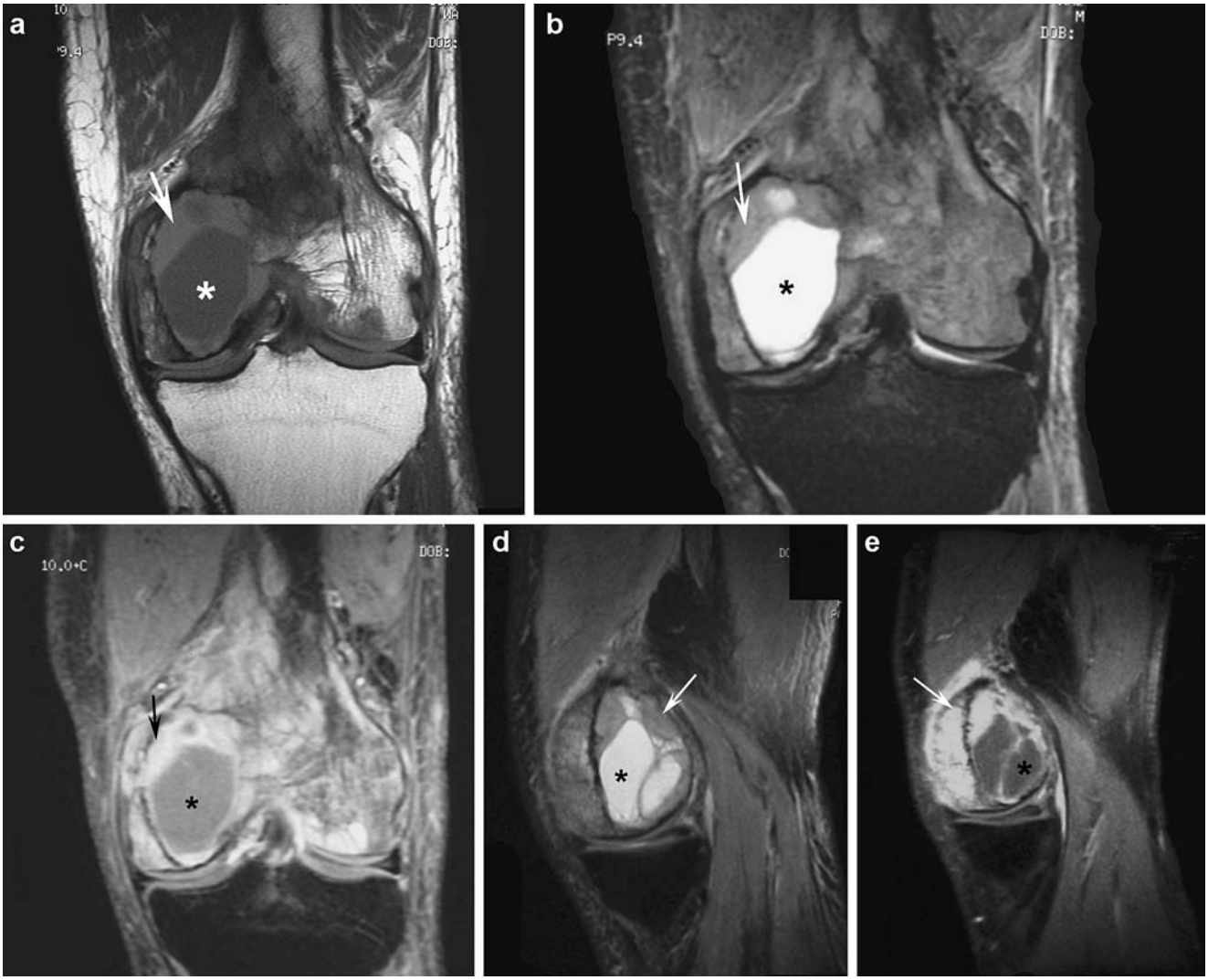


**Fig. 2** MRI of the distal femur. Coronal T1-weighted image, TE/TR 560/18 (**a**) shows coarse trabeculation and decreased SI in the medial femoral condyle (*arrow*). Note the low SI at the center of the lesion (*asterisk*). Coronal (**b**) and sagittal (**d**) short-tau inversion recovery (STIR) TR/TE 3,900/28E images show a lobulated mass lesion in the medial condyle (*arrow*) with increased SI at the center (*asterisk*). Following administration of contrast medium (**c**, **e**), enhanced SI is seen at the periphery of the mass (*arrow*). Note the lack of enhancement at the center of the mass following administration of contrast agent (*asterisk*), suggesting the presence of fluid

## Discussion

Paget disease of bone, first described by Sir James Paget as osteitis deformans, is a disease affecting the osteoclasts, occurs predominantly in populations of northern European descent, and is characterized by excessive osteoclast-mediated bone resorption followed by osteoblast-mediated bone formation. This osteoclastic–osteoblastic activity occurs in a seemingly haphazard fashion, resulting in abnormally remodeled bone. It is a slowly progressive disorder that is ultimately manifested by enlargement and deformity of the involved bones. Approximately 3% of the population aged over 40 years in the USA and the UK are affected by the disease. The incidence increases with age and, historically, has been reported to affect up to 10% of people above 80 years of age [7, 8]. However, for unclear reasons, the incidence of Paget disease seems to be on the decline. Paget disease is more common among men than women [9], and, although most cases are sporadic, familial forms have been described [10].

Radiographically and pathologically, Paget's disease may be divided into three phases, which, although commonly considered to be discrete and distinctive, actually represent a spectrum of changes seen in the disease [11]. The initial lytic phase is radiologically characterized by osteolysis, such as that seen in osteoporosis circumscripta of the skull, and is due to increased osteoclastic resorption as seen histologically. The second phase, the mixed phase, represents the majority of cases examined radiographically and is manifested as coarsening and

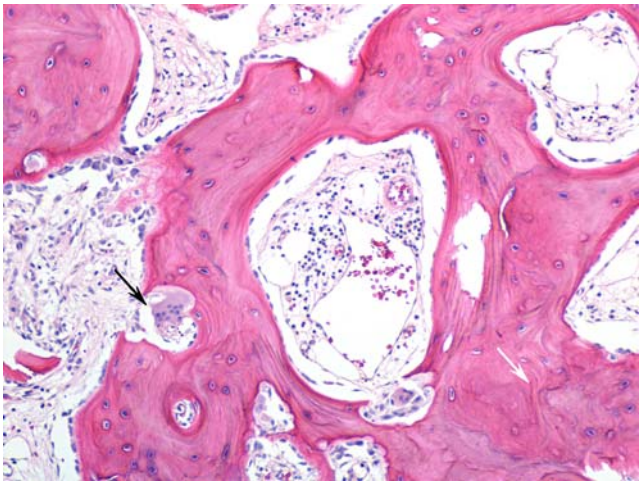

**Fig. 3** Trabecular bone with irregular cement lines (*white arrow*) lined by large osteoclasts (*black arrow*) and numerous osteoblasts with medullary fibrosis, typical histopathological findings of Paget disease

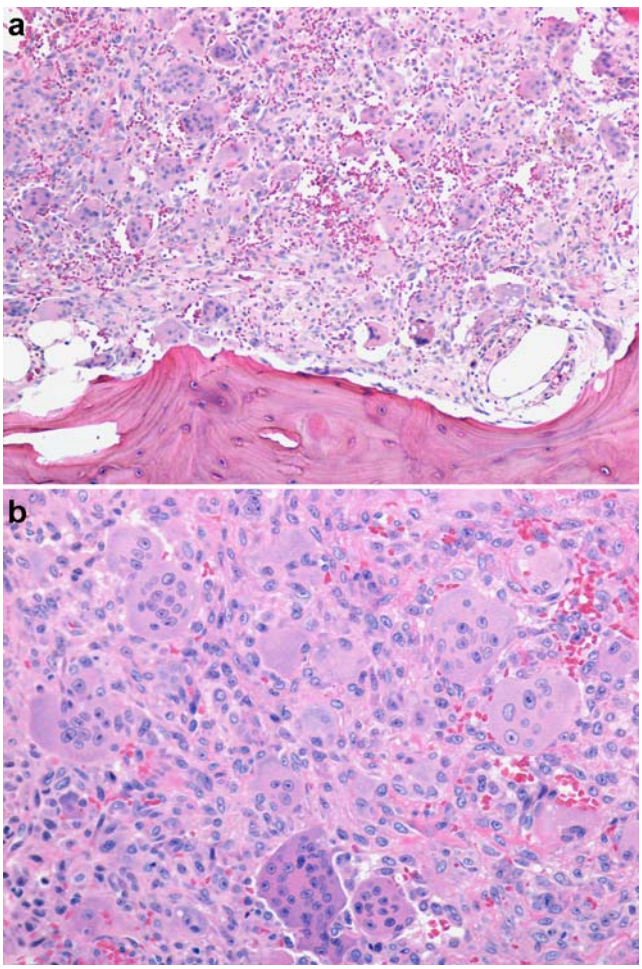


**Fig. 4** **a** Giant cell rich tumor (*top of image*) adjacent to bone with irregular mosaic-like cement lines (*bottom of image*). **b** Diagnostic field of GCT composed of sheets of large osteoclastic giant cells mixed with mononuclear cells with similar appearing nuclei supported by a rich capillary vasculature

thickening of trabeculae and cortex as a result of osteoblastic repair following oseoclastic activity. In this phase, trabeculae with irregular cement lines and woven bone are lined by osteoblasts and osteoclasts with marrow fibrosis. The third stage is termed the blastic stage, due to excessive osteoblastic activity in comparison with osteoclastic resorption and, therefore, is radiographically characterized by areas of sclerosis and enlargement of the bone. Histologically, this phase is characterized by thickened trabeculae with numerous cement lines often imparting a mosaic pattern.

In general, the primary cause of Paget disease is unknown. A viral etiology of Paget disease has been proposed for many years, based on the early discovery of viral-like intranuclear inclusion bodies in osteoclasts of Pagetic bone [12–14]. In addition, Mirra and Gold reported a case where viral-like intranuclear inclusion bodies were found in osteoclasts of giant cell tumor associated with Paget disease [15]. More recently, mutations in the gene encoding sequestosome 1 (SQSTM1/p62) have been identified in patients with familial and sporadic Paget disease [16]. This gene has been implicated in the signaling cascade involving RANK, which is essential to osteoclastogenesis [17]. Osteoclast precursors from patients with Paget disease seem to be hyperresonsive to RANK ligand (RANKL), and marrow stromal cells from pagetic bone show increased expression of RANKL [18]. The increased sensitivity of Pagetic bone to RANKL appears to be mediated by interleukin 6 (IL-6) [17]. Such findings suggest a genetic basis for the disease, which may depend on environmental exposure (virus) for the disease state to be manifested. One possible scenario would be that, within the pagetic bone micro-environment, osteoclast precursors, having been exposed to a virus, are hyperresponsive to RANKL. The osteoclasts produce increased levels of IL-6, eventually resulting in constitutive overexpression of RANKL in marrow stromal cells and osteoblasts further contributing to abnormal osteoclastogenesis in the Pagetic bone [17]. Furthermore, it is reasonable to postulate that such abnormal osteoclastogenesis could produce a giant cell tumor of Paget disease, possibly as a result of localized excessive osteoclastogenesis and associated stromal cell proliferation, or by autonomous proliferation of stromal and/or osteoclastic cells from additional molecular abnormalities.

Fewer than 10% of patients with Paget disease may suffer from discomfort or pain [9]. The major skeletal complications of Paget disease include fracture, osteoarthritis, and neoplasms. Malignant tumors, usually osteosarcomas or fibrosarcomas, develop in approximately 1% of cases [6]. In long-standing extensive polyostotic disease, malignant transformation may occur in 5–10% of patients [19–21].

GCT complicates Paget disease much less often than sarcomas do. A review of the Mid-America Tumor Registry between 1958 and 1983 found 82 cases of neoplasms arising in Paget disease of bone [21]. While the great majority of these tumors were osteosarcoma, only one case of GCT was identified. GCT of Paget disease may be single or multiple [11, 15, 22–24] and is usually benign, but a few cases of malignancy have been described in the literature that likely represent giant cell rich osteosarcoma [25]. Of note, Jacobs et al. [6] found five patients with benign GCT in Paget disease who had a common ancestral root in Avellino, Italy. A recent analysis of a large number of Italian patients with Paget disease showed higher clinical severity and greater frequency of neoplastic transformation among patients who lived in or were descended from individuals living in the Campania region of southern Italy. Our patient had no known ties with either to Avellino or Campania, Italy [26].

To our knowledge, 38 cases of GCT complicating Paget disease have been reported [6, 15, 27]. GCT, like Pagetic sarcomas, most commonly occur in the polyostotic form of the disease in over 90% of cases. Fewer than 10% occur in the mono-ostotic disease [28]. As in our case, the age of the patients is higher, with the mean age being approximately 60 years, while, in conventional GCT, it ranges between 20 years and 40 years [11].

Conventional GCT most commonly arises at the end of long bones. In contrast, GCT associated with Paget disease involves the skull, facial bones, pelvis or spine in accordance with the anatomic distribution of the underlying disease [6, 11, 27, 29]. Long tubular bone involvement is uncommon. Of the 38 cases of GCT in Paget disease, only seven (18%) involved long bones [30–34]. Whereas conventional GCT almost always involves the epiphyseal and metaphyseal regions of the bone, GCT of Paget disease involves only the metaphysis, diametaphysis or diaphysis in half of the cases [30–34].

On plain films, the lesion is lytic and may be expansile without a periosteal reaction and, in general, may resemble conventional GCT. A soft tissue mass is uncommon. The margins of the lesion are usually relatively well defined, which helps one to differentiate it from a malignant process. Rarely, the margins of the lesion will be sclerotic or poorly defined. Our tumor was lytic, with cortical disruption, and involved the epiphysis as well as part of the metaphysis.

MRI reveals a mass-like replacement of the marrow that is different from the alteration seen in the lytic stage of uncomplicated Paget disease [35]. As in this case, the signal intensity on both T1-WI and T2-WI appears low and remains heterogeneously low to intermediate due to the presence of cellularity and a fibrous component. Coexisting cystic and hemorrhagic components may present areas of higher signal intensity on T2-WI, as demonstrated in this case. Following administration of contrast agent, the tumor shows diffuse enhancement. CT and, particularly, MR imaging are essential in evaluating the extent of the tumor. Specifically, the demonstration of fat within a region of Pagetic bone on MRI effectively excludes the presence of tumor in that region of the bone [28]. Following steroid administration, the size of the tumor mass may decrease significantly, suggesting that soft tissue extension in Paget disease may not necessarily represent malignancy [6]. However, for a definitive diagnosis, surgical biopsy and pathology examination are required [1].

Histologically, GCT in Paget disease generally appears similar to conventional GCT. In addition to the diagnostic features of GCT, our patient had focal ABC-like change, corresponding to the fluid signal characteristics in the center of the lesion on MRI. One distinguishing feature of GCT in Paget disease is the presence of intranuclear inclusions, which we were unable to identify in this case by routine histological examination. Most importantly, one must distinguish GCT from a giant cell rich sarcoma. Sarcomas arising in Pagetic bone are typically high-grade tumors with marked cellularity, pleomorphism and atypical mitoses. In some cases of giant cell rich osteosarcoma cytological features of malignancy are subtle, and identification of neoplastic bone formation may be the major clue to malignancy.

Occasionally, GCT in Paget disease will histologically resemble giant cell reparative granuloma [36]. These lesions have clinicopathologic features similar to those of GCT of Paget disease, such as the presence of intranuclear inclusion in the giant cells and involvement of only Pagetic bone, with a preference for craniofacial bones. Both conventional GCT and Paget GCT can have regions within the tumor that are rich in fibroblastic spindle cells, with a paucity of giant cells, as was present focally in this case, and, therefore, it is conceivable that, in some tumors, this histologic appearance dominates and thereby resembles giant cell reparative granuloma. Given the clinicopathologic similarities between these two lesions, they likely represent ends of a morphological spectrum that can be seen with "GCT of Paget disease". Furthermore, the growing understanding of the etiology of Paget disease and the fact that these lesions occur in only Pagetic bone, even when multifocal, support the concept that GCT of Paget disease is biologically distinct from conventional GCT and giant cell reparative granuloma.

GCT complicating Paget disease has often been treated by surgical resection [27, 30–34]. Surgical curettage, as one would perform for conventional GCT, is a reasonable approach as well. Tumors may recur, but the overall prognosis is excellent. In our case, the tumor was curetted and packed. The patient has been free of symptoms and recurrent GCT for 24 months after surgery.

In summary, we present a case of mono-ostotic Paget disease complicated by the development of a benign GCT of the distal femur as the initial manifestation of the disease. The development of GCT in Paget disease is rare and particularly uncommon in long tubular bones. Although these tumors can have imaging features similar to those of conventional GCT, and histologically can have the appearance of conventional GCT or even giant cell reparative granuloma, the known underlying molecular abnormalities of Paget disease, and the growing understanding of the Pagetic bone micro-environment, suggest that these tumors are biologically distinct from conventional GCT and giant cell reparative granuloma. Biopsy should be performed to exclude a Paget sarcoma.

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