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Giant Cell Tumor of Bone

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Giant cell tumor (GCT) of bone is a benign but locally aggressive tumor that usually involves the end of long bone. Its histogenesis remains unclear. It is characterized by a proliferation of mononuclear stromal cells and the presence of many multinucleated giant cells with homogenous distribution. The name *giant cell tumor* was suggested by Cooper and Travers [1] in 1818. Virchow [2] suggested a malignant potential in 1846. Nélaton [3], a French doctor, was the first to recognize the similarities of the multinucleated giant cell with osteoclasts in 1860. In 1912, Bloodgood [4] reported on the benign nature of GCT. Most of current knowledge of this specific bone tumor has come from Jaffe and colleagues [5].

Clinical history

GCT has a significant incidence, accounting for 20% of all benign bone tumors and 5% of all bone tumors, malignant and benign [6]. Higher incidence has been reported for the Chinese population, in which it can be up to 20% of all bone tumors [7]. Although some series show a slight female predominance [6,8,9], most support that there is no sex predilection in GCT. GCT of bone most frequently occurs in young adults between 20 and 40 years of age (Fig. 1) [6,9,10]. Occurrence before epiphyseal plate closure is exceptional [6,8,11,122]. GCT can be seen in patients over 50 years old. Although less frequent, this disease needs to be included in the differential diagnosis process of a lytic bone lesion [6,12–17].

Ninety percent of GCT exhibits the typical metaphyseoepiphyseal location. Tumor often extends to the articular subchondral bone or even abuts the cartilage. The joint or its capsule is rarely invaded. In the rare instances in which GCT occurs in a skeletally immature patient, the lesion is likely to be found in the metaphysis [18,19].

The most frequent locations, in decreasing order, are the distal femur, the proximal tibia, the distal radius, and the sacrum (Fig. 2) [6,9,10]. Half of GCTs arise in the knee region. Other frequent sites include the fibular head, the proximal femur, and the proximal humerus. Spine involvement can be seen. The lesion is typically found in the vertebral body and usually spares the posterior elements. It is also eccentric, which is helpful in differentiating it from chordoma [9,20–22] (this is especially true for sacral location). Pelvic GCT is rare [119,120]. Iliac or sacral GCT can cross through the sacroiliac joint to involve the adjacent bone. The tarsal bone is another significant location for GCT, but phalanx, metatarsal, metacarpal, and maxilla are rarely involved. Giant cell reparative granuloma is a frequent tumor in these locations and closely resembles GCT radiographically and histologically. Rare cases of GCT of cranial

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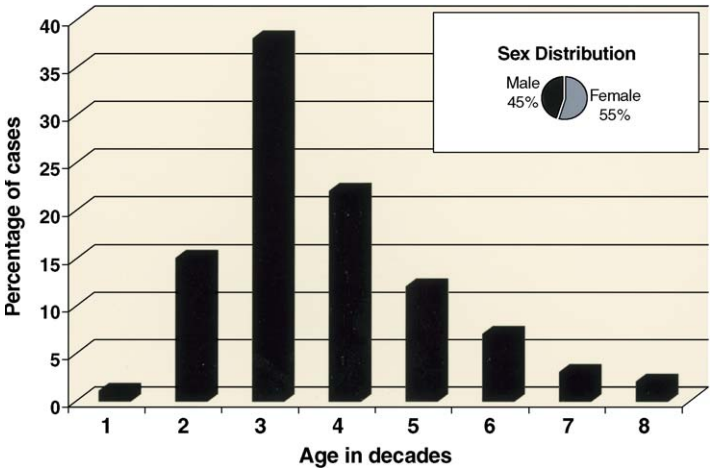


Fig. 1. Age and sex distribution in 1229 cases of GCT of bone from a collection of series by Campanacci [8], Huvos [9], and Unni [6].

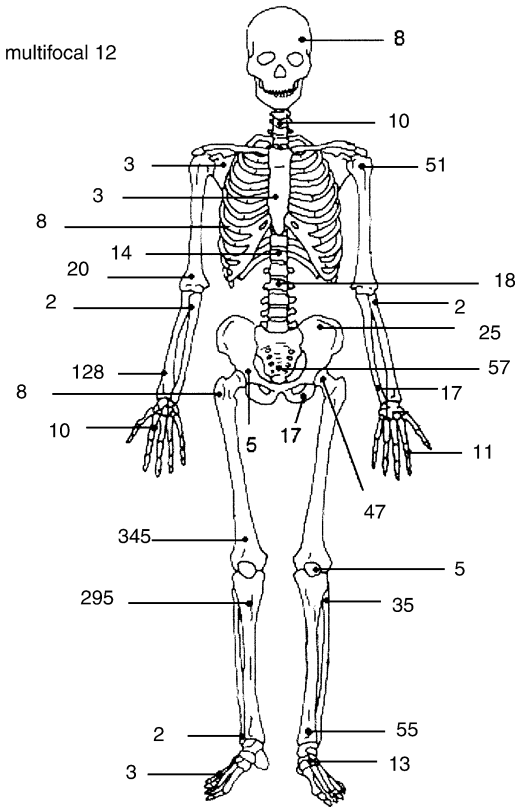


Fig. 2. Anatomic distribution of 1229 GCT of bone from a collection of series by Campanacci [8], Huvos [9], and Unni [6].

bone have been reported and are most often associated with concomitant involvement of the bone by Paget's disease. It is interesting that multiple foci of GCT can be seen within the bone in these instances [13,14,16,25,26]. In addition to this association, multicentricity or the synchronous occurrence of GCT in different bones is known to occur but is exceedingly rare [6,27,28]. Metachronous or sequential occurrence of GTC in different bones is anecdotal but associated with location in the hand or foot when the GCT involves the metaphyseodiaphyseal portion of a long bone. The time interval between the appearance of the first and the subsequent lesions can be many years [29,30]. When facing multicentricity in GCT or if the clinicoradiographic features appear unusual, one should suspect dealing with brown tumor of hyperparathyroidism. Histologically, both lesions are rich in giant cells, which could be confusing. When any clinical doubt exists, patients should be tested for serum calcium, phosphorus, and parathyroid hormone levels.

Pain is the leading symptom in GCT and relates to the mechanical insufficiency resulting from bone destruction, which predisposes patients to fracture. Pathologic fracture is seen in about 12% of patients at the time of diagnosis (Figs. 3A, 4A) [31,32]. A bump or a soft tissue mass can occasionally be seen and results from the cortical destruction and tumor progression outside bone. Because GCT is often found close to the joint, limited range of motion is frequently noticed. Joint effusion and synovitis are also possible. Spinal GCT often has an insidious onset of progressive neck or low back pain. Associated neurologic deficits with these tumors are

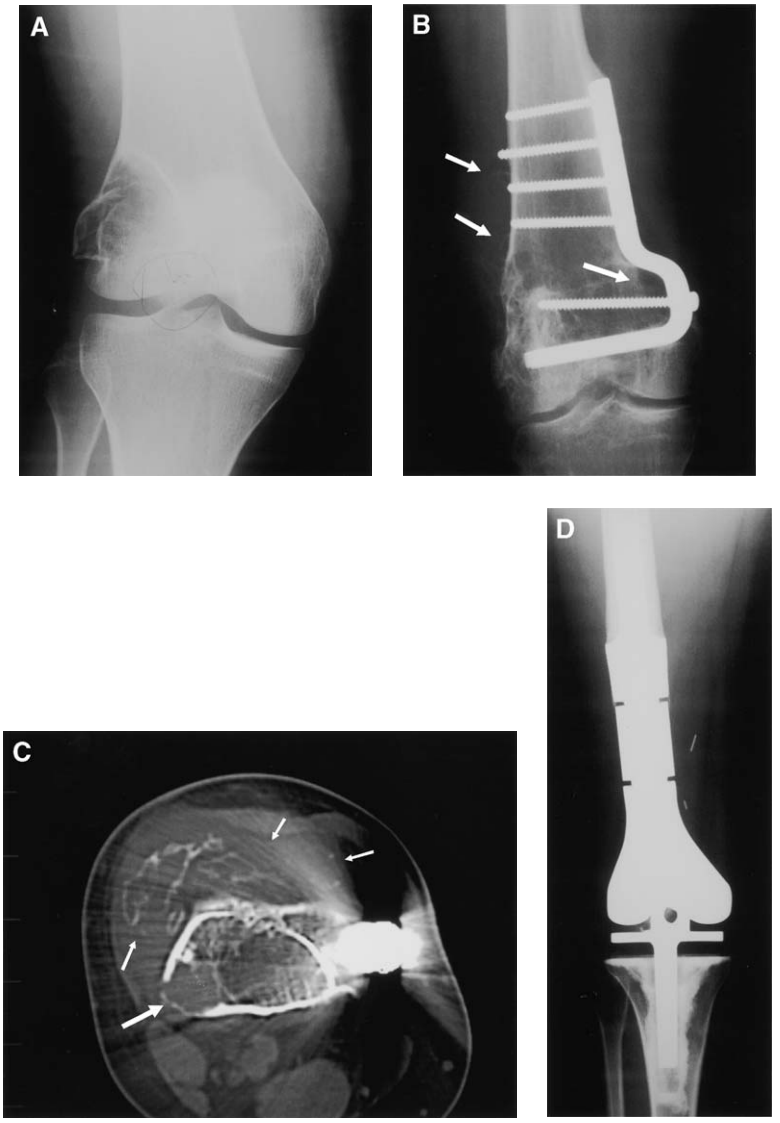


Fig. 3. (*A*) Stage 2 GCT of lateral femoral condyle in a 24-year-old woman showing an intra-articular displaced fracture. Patient was treated in a community hospital with curettage and grafting. A valgus malunion persisted. (*B*) Following bone healing, patient underwent a supracondylar varus osteotomy. Sixteen months following initial surgery, however, she presented with multiple areas of local recurrence (*arrows*). (*C*) CT scan showing areas of recurrence in bone (*large arrow*) and soft tissue (*small arrows*). Note the typical appearance of GCT soft tissue recurrence: nodules devoid of matrix circumscribed by a thin peripheral layer of bone. (*D*) Definitive cure was achieved with a distal femoral replacement showed at 4 years post surgery.

not exceptional, possibly leading to the presumptive diagnosis of disk herniation [26,33–35].

Radiology

Radiographically, GCT of bone displays features that are somewhat characteristic and help in the establishment of a presumptive diagnosis. GCT is usually purely lytic and eccentric within the bone (Fig. 5). As previously stated, in long bones, it is found in the metaphyseoepiphyseal region. The tumor appearance is geographic, with ill-defined borders and often without any identifiable sclerosis. Cortical and cancellous bone likewise appear destroyed. Although aggressive appearing, a permeative pattern of bone

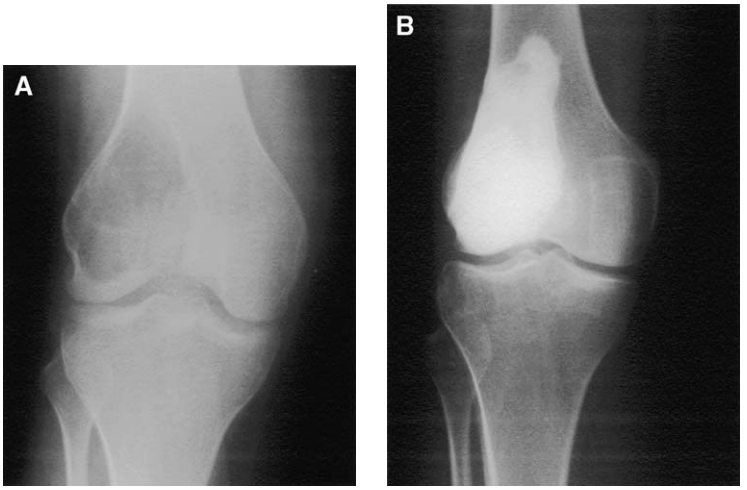


Fig. 4. (*A*) Plain anteroposterior radiograph of the right knee in a 22-year-old woman with a stage 2 GCT complicated by a minimally displaced intra-articular fracture of the lateral femoral condyle. (*B*) Following extended curettage, open reduction and internal fixation was achieved with the use of cement.

destruction is unusual. Bone contour can be expanded with faint and thin periosteal new bone formation. Pseudoseptations are often noted on plain radiographs and are the result of the uneven bone destruction in three dimensions. Tumor matrix is devoid of any ossification or calcification and of similar density to the surrounding soft tissues. CT scan shows the cortical involvement and the soft tissue extension when it exists (Figs. 6B, 7B). The best imaging of full tumor extension is provided, however, by MRI (see Figs. 6C,D and 7C) [36].

Plain radiographs are most helpful in the differential diagnosis that includes GCT. Involvement of the metaphyseoepiphyseal area in a long bone is known to occur most often for three types of bone tumors. GCT is the most frequent, followed by chondroblastoma and, much less frequently, clear cell chondrosarcoma. Chondroblastoma usually occurs in skeletally immature patients. Lesions frequently have a sclerotic rim, and calcifications are seen within the matrix in about 40% [37]. Clear cell chondrosarcoma is found mostly in femoral and humeral heads of young adults. It shows peripheral sclerosis and matrix calcifications and is difficult to distinguish from chondroblastoma before biopsy. Aneurysmal bone cyst (ABC) is another tumor that can look similar to GCT. Although it most often involves the metaphysis of long bone, it is usually devoid of matrix calcifications and peripheral sclerosis. ABC margins are often imprecise, and expansion of the involved bone is usually more marked than in GCT.

GCT, ABC, chondroblastoma, and clear cell chondrosarcoma share the common feature of being eccentric within the bone. Other tumors that should be included in the differential diagnosis are osteosarcoma when it is very lytic or the giant cell–rich variant, malignant fibrous histiocytoma, fibrosarcoma of bone, and plasmocytoma. Metastatic carcinoma should also be considered in the older age group although bone metastases are usually located in the metaphysis or diaphysis of long bones and are less eccentric [38–40].

Similar classifications of GCT based on radiographic appearance were described by Enneking [41] and later by Campanacci [8]. These investigators described three stages that correlate with tumor local aggressiveness and risk of local recurrence. Stage 1 is the least frequent and shows features of latent or slow-growing tumor. The size of the lesion is small, with a mild amount of sclerosis delineating the tumor. Bone contour is not affected, although the cortex can be thinned. The tumor does not extend to the articular cartilage. Symptoms are absent or minimal and of long duration. Stage 2, noted in 75% of GCT at presentation [42], shows features of an active lesion with ill-defined borders and without sclerosis. The cortex is thinned if not breached and deformed with expansion, and the periosteum is elevated. The tumor often extends to the articular cartilage from within the marrow (see Fig. 5). Stage 3 shows extreme aggressiveness, with a tumor of large volume that destroys bone and invades the surrounding soft tissues.

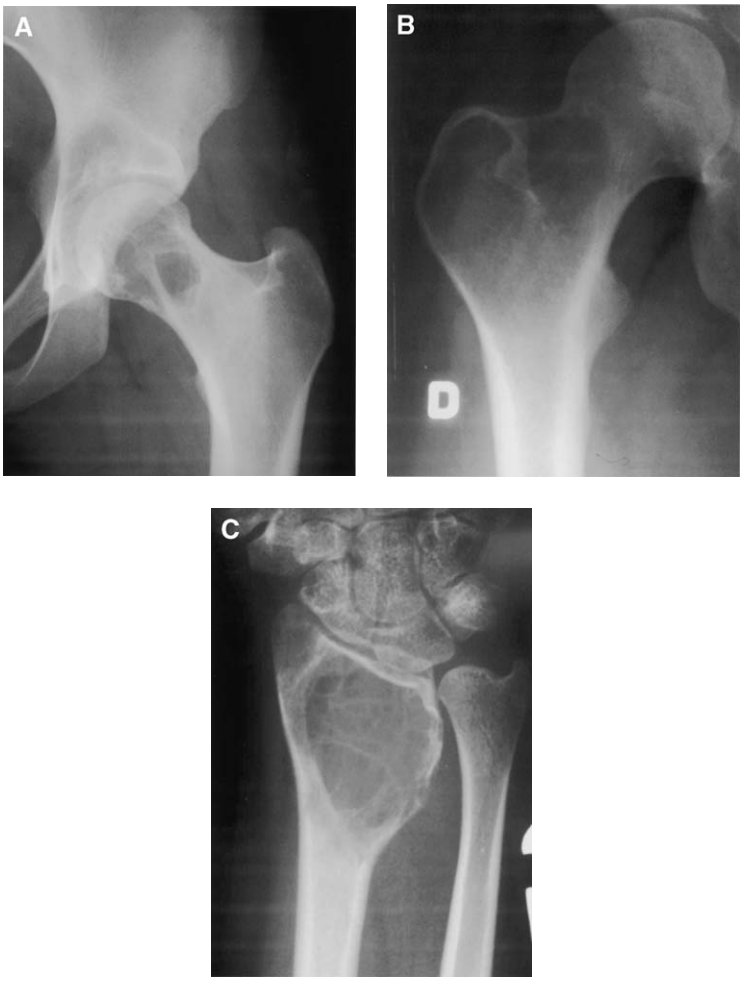
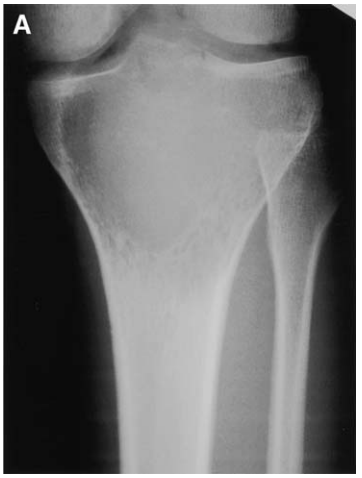


Fig. 5. Plain anteroposterior radiographs showing the typical appearance of stage 2 GCT of bone. (*A*) Femoral head. (*B*) Greater trochanter. (*C*) Distal radius.

Tumor boundaries are imprecise, with possible permeation, which can be suggestive of a malignancy. The tumor abuts the articular cartilage (see Figs. 6 and 7). Tumor growth can be rapid. Higher local recurrence rates are reported with stage 3 tumors and more frequently seen in locally recurrent tumors than in primary presentation (see Fig. 3).

Staging

Although radiographic findings may suggest GCT of bone, as for any suspicious bone lesion, a full staging strategy is highly recommended. This strategy could include a CT scan or MRI of the affected area to evaluate the full local extent of the lesion, a total body bone scan to rule out additional asymptomatic bony lesions, and a chest radiograph to exclude lung involvement. Basic blood work can be obtained, although no specific abnormalities are expected. If hypercalcemia and or hypophosphatemia were recorded, then brown tumor and hyperparathyroidism should be high on the differential diagnosis. A biopsy is mandatory to confirm the diagnosis and can be achieved with a core-needle or open biopsy. Principles of musculoskeletal tumor biopsy should be adhered to and (1) include a direct approach in line with the projected incision if a resection is to be performed following the discovery of malignancy; (2) should be vertical, muscle splitting; and (3) the bone window should be oval and good hemostasis should be achieved before wound closure. In centers that have a special interest in bone tumors, the biopsy is often set up to be followed immediately with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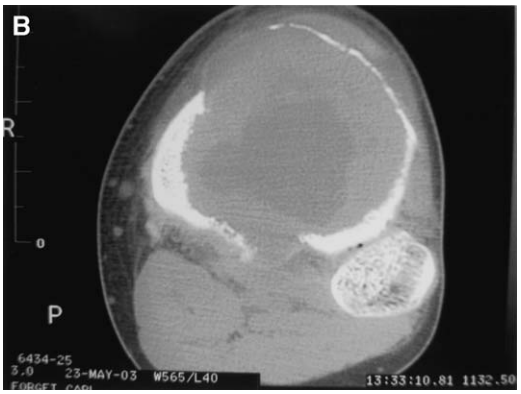
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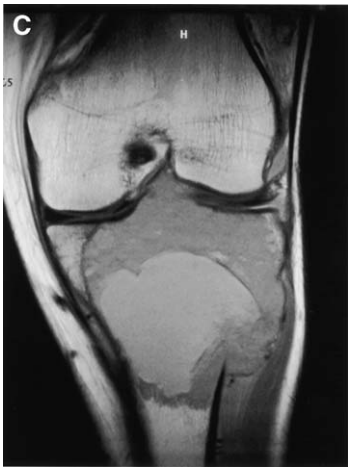
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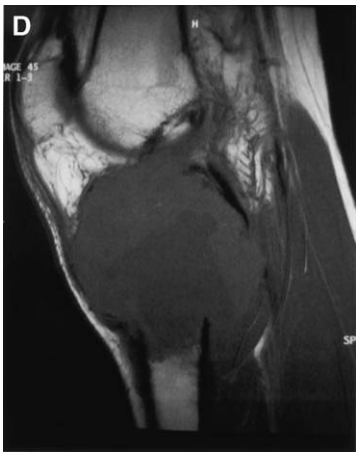
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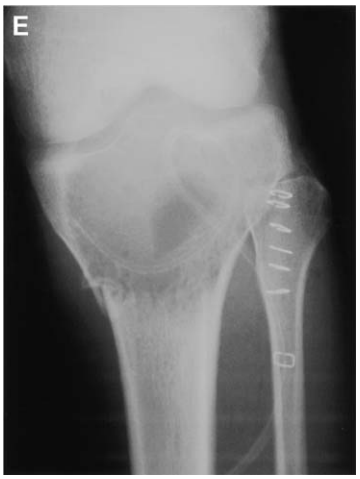
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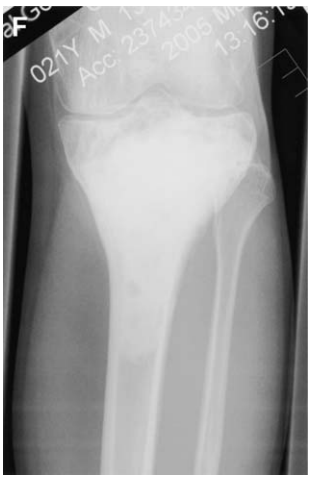
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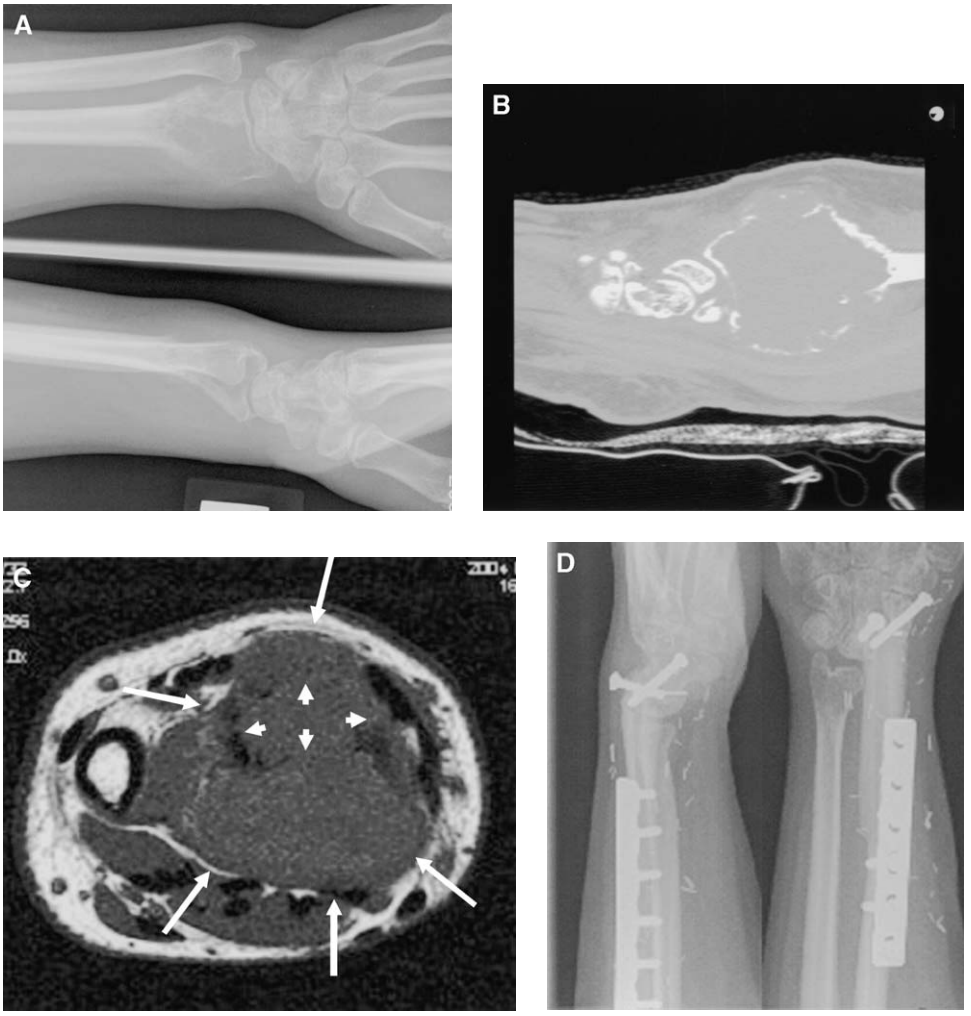

Fig. 7. (*A*) Anteroposterior (*top*) and lateral (*bottom*) plain radiographs of a 20-year-old woman with a stage 3 GCT of distal radius. (*B*) CT scan of sagittal reconstruction showing subchondral bone erosion, deformation, and soft-tissue extension. (*C*) Axial MRI cut shows remains of the original outline of distal radius (*arrowheads*) and extensive soft tissue involvement (*long arrows*). (*D*) Lateral (*left*) and anteroposterior (*right*) radiographs showing results of en bloc resection and reconstruction that used a vascularized fibula to achieve fusion to the proximal carpal row.

curettage if frozen sections confirm the diagnosis of a benign GCT. Interpretation of frozen sections can only be done safely if an experienced bone tumor pathologist is available and good communication exists between the surgeon, the radiologist, and the pathologist. When frozen pathology findings are unusual or not in keeping with the radiologic findings (even if it most likely resembles GCT on radiographs), surgery should be delayed until final pathology is available.

At the time of surgery, the cortex is often thinned and perforated in areas. The periosteum can be intact

Fig. 6. Plain radiograph (*A*), CT scan (*B*), and MRI (*C*,*D*) showing a large stage 3 GCT of proximal tibia in a 20-year-old man. (*E*) Open biopsy was complicated by pathologic fracture and became infected. These complications precluded the initial treatment plan of proximal tibial resection and reconstruction with an osteoarticular allograft. (*F*) Packing with antibiotic-loaded cement was performed after extended curettage. Patient has good function 15 months post surgery without evidence of recurrence of infection or tumor.

except in those cases (stage 3) in which it may be absent and the tumor extends into the surrounding soft tissues. Tumor margins are usually well defined in the medullary canal, and small pockets of tumor can be found in cancellous bone with extensions from the main cavity that can easily be overlooked and lead to recurrence. Satellite lesions are rarely expected.

The tumor typically appears red-brown on gross examination. GCT is very vascularized, and hemorragic changes and lipidic degeneration can be encountered. Invasion of ligaments by the tumor is possible. Articular cartilage is usually preserved, even if the subchondral bone has disappeared, and extra care must be taken during curettage. Intra-articular extension of GCT remains exceptional, even in cases of pathologic fracture.

Histology

GCT shows increased cellularity, with numerous multinucleated giant cells uniformly dispersed among a large population of mononuclear cells that are important for diagnosis (Fig. 8). There is little or no intercellular substrate other than a few collagen fibers. Mononuclear cells can be round, oval, polygonal, and sometimes spindled. They exhibit little cytoplasm. The nuclei contain one or more nucleoli and can exhibit variable amounts of hyperchromasia that is different from malignancy. Mitotic figures can be numerous but devoid of abnormalities. The multinucleated cell population exhibits a large volume and their centered nuclei may contain more than a hundred nuclei. These nuclei closely resemble the nuclei of the mononuclear cells. The cytoplasm of the giant cell is abundant and can contain vacuoles. Numerous blood vessels and capillaries are found, as are areas of necrosis. Reactive bone trabeculae can be seen but is usually at the periphery of the tumor. Intravascular invasion by GCT cells is frequent and more likely seen at the periphery of the lesion. It does not correlate with the incidence of metastasis. Areas of ABC can occur in association with GCT and are seen as blood-filled cavities devoid of endothelial cells.

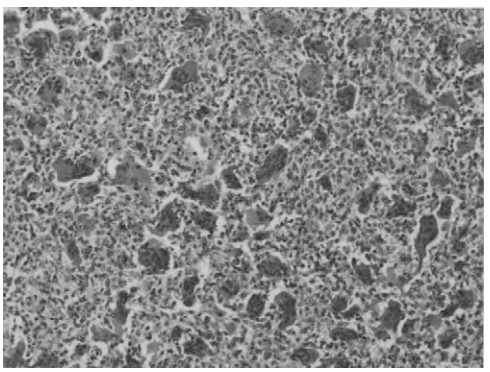

Fig. 8. Typical histologic appearance of benign GCT showing hypercellularity with a population of mononuclear cells and numerous giant multinucleated cells uniformly dispersed.

On histology, the differential diagnosis must include giant cell reparative granuloma and brown tumor of hyperparathyroidism. Both show a more fibrous stroma with multinucleated giant cells containing less nuclei and having a more irregular distribution than in GCT. ABC also shows a smaller number of multinucleated cells with a more fibrous stroma but, strikingly, contains large areas of vascular cavities devoid of endothelial cell lining. Areas of ABC changes can often be identified in GCT. Large sampling is necessary, along with careful review of the radiographs, to make sure that one is not dealing with GCT or other tumors known to be associated with ABC changes when a diagnosis of ABC is made on histology. Giant cell–rich osteosarcoma is a rare variant of osteosarcoma. As its name implies, it shows a large number of multinucleated cells. Its striking feature is the presence of small, malignant, mononuclear cells exhibiting significant atypia and the production of malignant osteoid, albeit often in minimal quantity [6].

Historically, GCT was graded in three histologic grades that are now of little use because they do not correlate with prognosis [8,9]. Giant cell sarcoma is a very rare primary tumor, most frequently associated with recurrence of tumor or following irradiation. Sufficient biopsy sampling is necessary in GCT because sarcomatous areas may exist throughout areas of a benign-looking lesion.

Basic sciences

There is evidence that three types of cells are found in benign GCT of bone [43]. Type I cells look like interstitial fibroblasts, make collagen, and have the capacity to proliferate. This cell population is likely the tumor component of GCT [43]. Type I cells share some features of mesenchymal stem cells from which they could be derived; however, they possess features that suggest they could represent an early differentiation of mesenchymal stem cells into osteoblasts [28,44–46,123]. Type II cells are also interstitial but resemble the monocyte/macrophage family and could be recruited from the peripheral

blood stream [47]. These cells are thought to be precursors of the multinucleated giant cells (by fusing together or by nuclear multiplication without cell division). Type II cells express surface receptors of the monocyte/macrophage lineage but these receptors are not found on giant cells [43]. Type III cells are the multinucleated giant cells. They share many characteristics of osteoclasts and have similar morphologies [48]. They possess enzymes for bone resorption, including tartrate resistant acid phosphatase and type II carbonic anhydrase [49]. GCT giant cells exhibit most of the specific osteoclast antigens [50,51]. Cell receptors for calcitonin and vitronectin are present [43], and expression of matrix metalloproteinases (MMPs) is found [52].

Significant-level activity for insulin-like growth factor I and II is found in type II and type III cells but absent in type I cells, which suggests that these factors are important in the development and regulation of GCT [53]. In addition, it is known that insulin growth factor I plays a role in the formation of osteoclasts from monocytes, augments osteoclast level of activity [54,55], and increases bone resorption [56,57]. Transforming growth factor (TGF)-β1, found in all three cell populations of GCT, is thought to be implicated in the recruitment of the multinucleated cells or their precursors. TGF-β2 is found only in multinucleated cells [58]. MMPs (MMP-9 and MMP-2) are enzymes that act on extracellular matrix and collagen degradation. Tissue inhibitors of metalloproteinases, such as TIMP-1, regulate their activities. MMP and protease activity increases in GCT as the radiographic grade or clinical aggressiveness (such as lung metastases) increases [39,59]. MMP-9 is mostly found in the multinucleated giant cells [52,60,121]. Cathepsin K is also only found in the multinucleated giant cell population [60]. These findings suggest that bone resorption in GCT is achieved through the action of the osteoclast-like giant cells. No specific translocation or chromosomal anomalies are found in GCT, but normal karyotype is rarely encountered. Telomeric fusion, or fusion of two chromosomes by their ends, is a frequent finding compared with other solid tumors. It most often involves chromosome 11. A higher incidence of chromosomic anomalies has been reported for recurrent benign GCT or GCT that metastasizes to lung (97%) than for GCT cured after initial surgery [10].

Treatment

GCT of bone is benign and most frequently involves the end of a long bone adjacent to a joint in a young adult. The best treatment should insure local control and maintain function. Curettage has been the preferred treatment for most cases of GCT. Historically, local recurrence rates of 25% to 50% have been reported (see Figs. 6 and 8) [6–8,13,14,16,19,61–64]. The most recent series that have included modern imaging techniques and extended curettage through the use of power burrs report improved local recurrence rates (10%–20%) [23,65–67]. In due consideration, it is preferable to have a conservative approach because most patients can be cured with such curettages, even if reoperation is required.

The recommended curettage technique involves the opening of the bone through a large cortical window that allows visualization of the entire tumor cavity. The use of a headlamp and dental mirrors allows vision of areas difficult to reach directly. Curettes of different sizes allow for curettage of the cavity and the smaller pockets of tumor. After curettage is achieved, the cavity is deepened with the use of high-speed burrs.

Various investigators have proposed the use of local adjuvants in an attempt to achieve a local recurrence rate less than 20% [25,42,63,68]. Phenol [11,22,68,69], liquid nitrogen [70,71], bone cement [62,63,68,72], hydrogen peroxide [21], zinc chloride [73], and more recently, argon beam cauterization have been employed. Chemical or physical agents work by inducing an additional circumferential area of necrosis to "extend" the curettage. Antineoplastic agents such as methotrexate or adriamycin have been studied in addition to cement [74,75]. No clear evidence exists as to whether adjuvants are effective [76], but from retrospective studies, liquid nitrogen has achieved the highest cure rates. Safe handling of liquid nitrogen is difficult, and significant fracture rates have been reported [70,71]. Although the usefulness of bone cement as an adjuvant has recently been questioned [23,64–67,77], there are many advantages to support its use as a cavity filler: (1) it provides immediate mechanical stability, allowing for early weight bearing; (2) it allows for early detection of recurrence [78,79]; and (3) it may have a cytotoxic effect on tumor cells (usually at the cement–bone interface) through the methylmetacrylate monomer and the energy dissipated as the cement sets (cement can induce heat necrosis a few millimeter deep in adjacent bone) [80,81]. Although it appears that cement may be tolerable just underneath the joint surface (Fig. 9C) [82,83], reports have suggested that cement should not be placed deep into the exposed cartilage. Interposing a centimeter or two of bone graft between the cartilage and the cement may

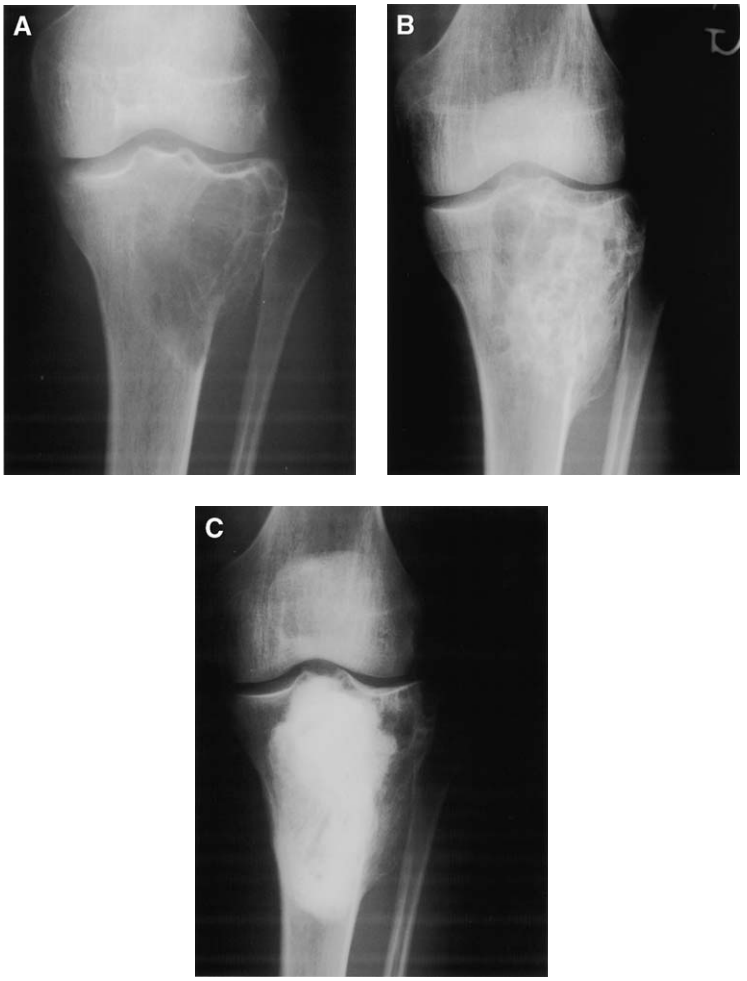

Fig. 9. (*A*) A 25-year-old man who had GCT of proximal tibia treated with curettage and grafting. (*B*) Twelve months later, local recurrence becomes visible on the medial side and under the tibial spines. It is not always easy to detect recurrence with plain radiographs early on because of the bony changes associated with previous treatment and healing. (*C*) Anteroposterior plain radiograph 10 years after additional curettage and cementing.

reduce heat damage and the resultant early degenerative changes [8,84]. Nonetheless, studies have shown that cement constructs are less rigid than normal subchondral bone or successful bone graft [85,86]. In cases of pathologic fracture, cement can also be used to provide a solution to maintain reduction and stability in the fractured eggshell-like cavity (see Fig. 4) [31].

Most recurrent tumors can be treated like primary ones, with extended curettage and grafting or cementing (see Fig. 9) [61,68]. For extensive recurrences, sometimes a sarcoma-like wide resection and reconstruction is indicated (see Fig. 3). The incidence of soft tissue recurrence has been reported to be about 1% [87]. It characteristically appears as a growing nodule, with an incomplete peripheral rim of bone and a center devoid of specific matrix (see Fig. 3C) [8,87,88]. The same phenomenon is sometimes seen with lung metastases from benign GCT. It is strange that these recurrent tumors do not show osteoid above production bone within the lesion. TGF-β1 and TGF-β2 are known to be present in GCT and are involved in the differentiation into osteoblasts of mesenchymal cells originating from adjacent tissue. These TGFs could be responsible for peripheral bone production [88]. It is interesting that intra-articular recurrence of GCT appears to be exceedingly rare, if it ever occurs, even following pathologic fracture.

Wide en bloc resection is known to provide the lowest recurrence rate [25,42,61,89]. This practice is often debatable in the context of benign tumor [67] but can be considered in expendable bones such as the fibula or clavicle. Many stage 3 tumors are treated with such resections, as are multiple local recurrences or pathologic fracture when joint anatomy cannot be restored (see Figs. 3 and 7) [67]. Wide resections/reconstructions can affect function permanently; their results are difficult to compare with conservative surgery because the indications are usually different [61,67]. Reconstruction is achieved as in bone sarcomas, with the use of fibular transfer [90], allograft, endoprosthesis, or arthrodesis (see Figs. 3, 6, and 7); amputation is rarely considered. A more aggressive surgical approach has been recommended by some investigators for GCT arising in the distal radius because local control is more difficult to achieve in this location [23]. Others disagree with this approach and believe that the radius should be treated like any other long bone [67,91]. For large proximal tumors or for difficult locations such as the pelvis, sacrum, and spine, it is wise to proceed with preoperative embolization to minimize bleeding, which can be significant. Embolization may also be attempted to limit progression of an inoperable recurrent tumor. This method of treatment has been reported following repeated embolizations in difficult locations such as the sacrum [92].

Radiotherapy has been used to treat GCT [3,35,93–95]. It is useful especially in difficult locations such as the spine and sacrum. It has also been advocated to decrease local recurrence. The long-term risk of malignant GCT or postradiation sarcoma has limited its routine use [8,35]. The commonly used dosage is 40 to 45 Gy because total dosage beyond 50 Gy has been associated with a higher risk of malignancy. Use of megavoltage instead of orthovoltage has been reported to not induce sarcomatous changes [95,96]. No formal criteria exist to measure response of GCT to radiation; however, improvement of symptoms, decrease in pain, and progressive ossification suggest a favorable response.

Most local recurrences occur between 12 and 18 months after surgery and rarely after 3 years [8,67]. Local recurrence should be suspected when a progressive area of radiolucency appears within or adjacent to the previously treated area. These areas are more identifiable on plain radiographs when cement has been used as a filler than when bone grafts are used (bone graft healing shows sclerotic and lytic areas; lysis is due to graft resorption) (see Fig. 9). Symptoms appear later as the tumor reaches a significant size. Repeated curettage, even in a multiply recurrent lesion, allows for cure in 80% to 90% of GCT cases without the need for resection. Recurrence rates are still 5% to 10% following resection.

Biphosphonates are drugs that inhibit bone resorption by the osteoclasts. Recent evidence suggests that these agents may have an effect on the giant cell population of GCT by inducing apoptosis and possibly limiting tumor progression [20,97,98]. If confirmed with in vivo and clinical studies, then biphosphonates may offer a novel solution in the treatment of benign GCT of bone and the rare but difficult to treat lung metastases.

Function

Long-term functional results are usually very good after the treatment of GCT, even after curettage and grafting or cementing [66,67]. Pathologic fracture through a GCT may be associated with persistent pain and lowered functional scores.

Lung metastasis from histologically benign giant cell tumor

Although it may seem odd to link lung metastases, a behavior usually associated with malignancy, to a benign bone process, it has been observed by many investigators [17,77,99–107]. The estimated incidence of this phenomenon is 3% [63]. On histology, the lung metastases are identical to benign GCT of bone. Increased incidence of lung metastases is associated with location of primary tumor in the distal radius or sacrum, stage 3 lesions, and multiple local recurrences [16,35,63,77,100]. Dissemination appears to be hematogenous and could happen during curettage, but this remains unproved [9]. Multiple chest nodules, a rare phenomena, may be present but must be confirmed histologically, which can be performed through transthoracic needle biopsy or thoracoscopy or thoracotomy. The latter technique is usually preferred because it allows for full tissue sampling and complete removal of lesions when feasible. If sarcomatous, then this should raise the suspicion that the primary bone tumor was malignant.

It is difficult to predict the behavior of these metastatic benign lesions of the lungs. Spontaneous regression and disappearance have been reported [77]. Progression is usually slow. Reports have suggested up to 70% survival following aggressive

management of lung metastases with repeated surgery [45,77]. For this reason, it is usually wise to resect them early when possible. In cases in which lung lesions are unresectable or rapidly recurrent or multiple, chemotherapy (including interferon) [108] or radiotherapy could be an option, but their usefulness remains to be confirmed [100,109]. Mediastinal lymph node involvement has been reported, and treatment should be the same as for lung nodules [110].

It is clear that current histologic classification cannot identify benign-looking GCT that has a more malignant behavior. In the near future, molecular biology may lead to a new classification of GCT that will allow clinicians to tailor treatment modalities and follow-up studies according to the specific risk of each tumor.

Malignant giant cell tumors

Malignant GCT or giant cell sarcoma is rare [24,111–116]. Large series report an incidence of 5%. Spontaneous primary malignant GCT seems exceptional. Malignancy showing as a recurrence of a previously benign GCT is occasionally seen fol-

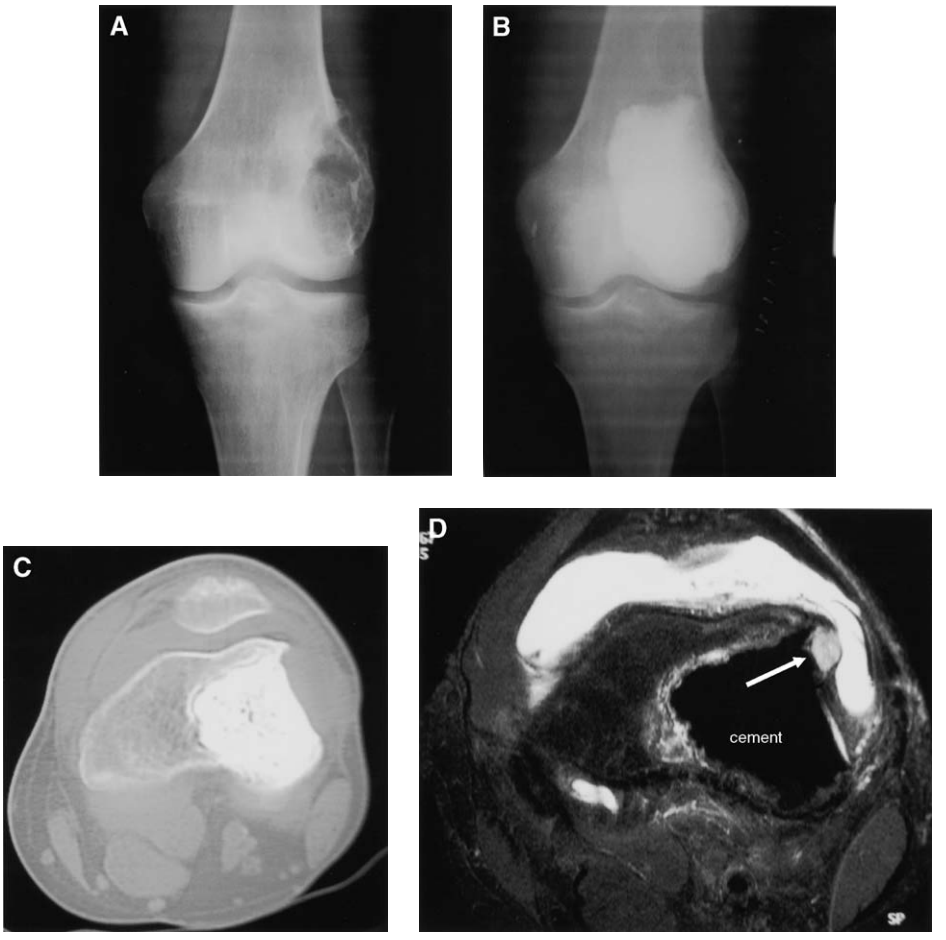

Fig. 10. A 54-year-old man who underwent curettage and autografting of a GCT of lateral femoral condyle in 1969. (*A*) Patient became symptomatic in 2001 3 months before this plain radiograph was taken. Although suspected, malignant recurrence could not be diagnosed on histology even after additional outside consultation. (*B*) Anteroposterior plain radiograph following extended curettage and cementation. (*C*) CT scan and (*D*) MRI showing local recurrence (*arrow*) at periphery of cement 12 months after initial treatment, this time found malignant on histologic sections. (*E*) Treatment included neoadjuvant chemotherapy and distal femoral resection. Metastatic chest nodules developed 9 months later and were resected. Patient is currently free of disease 1 year post thoracotomy.

lowing curettage and without previous use of radiation (Fig. 10). The most often encountered scenario is a recurrent malignancy 1 to 10 years or more after irradiation of a previously benign GCT. A dosage as low as 40 Gy could trigger this transformation. This dosage is less than 50 Gy, which is usually recognized to be sufficient to induce postradiation sarcoma, and suggests that benign GCT cells might be prone to malignant transformation. The term *malignant GCT* is controversial because some investigators use it only when there is coexistence within the lesion of areas typical of benign GCT with other areas of frank malignancy changes [117]. It is looked at as areas of dedifferentiation and named according to the morphology of dedifferentiated tissue such as osteosarcoma, malignant fibrous histiocytoma, or fibrosarcoma [118–123]. Malignant GCT is treated like sarcoma (with neoadjuvant chemotherapy and wide resection), achieving a cure rate of 75%. Lung metastasis remains problematic and is addressed with chemotherapy and thoracotomy.

Follow-up

Due to the high incidence of local recurrence and the risk of lung metastasis, a close follow-up of patients who have GCT of bone is required. Follow-up appointments after treatment should be every 3 or 4 months and should include physical examination and plain radiographs of the involved bone. This follow-up allows for early detection of any recurrence. CT scan or MRI can be of great help when recurrence is suspected. It is unclear whether these imaging modalities have any role for routine follow-up evaluation. Follow-up can be extended to every 6 months after 2 or 3 years. Yearly visits after 5 years up to year 10 are usually recommended. There are no clear recommendations regarding chest surveillance. Chest radiographs should probably be done at every clinic visit. Although a CT scan of the chest may allow for earlier detection of nodules, the low incidence of lung metastasis precludes its routine use. CT scans may be preferred initially, at time of diagnosis, as part of the staging process.

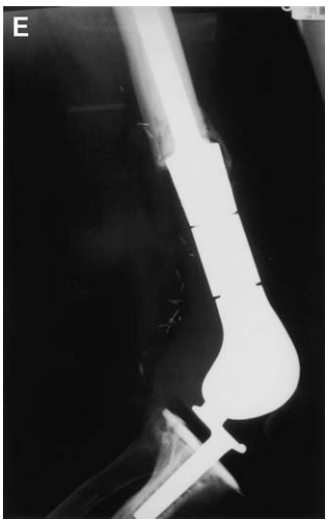

Fig. 10 (*continued*).

Summary

GCT of bone is a lesion with unpredictable behavior. It presents as a lytic defect in the end of long bone, most frequently affecting the knee area. Although benign, it is locally aggressive and deserves specific treatments that result in decreased local recurrence and preservation of function. Extended curettage followed by cement or bone grafting of some kind is the most often used treatment. En bloc resection is rarely a necessity and is used for more aggressive lesions when the bone or joint surface cannot be salvaged. With modern staging and treatment, the overall local recurrence rate is between 10% and 20%. Local recurrences are usually treated in the same manner as primary tumors. Lung metastasis from benign GCT of bone exists and should be treated vigorously. Malignancy is rarely associated with GCT but may be found in a recurrent tumor (suggesting an initial wrong diagnosis) or years after irradiation of a previously benign GCT. Malignant tumors should be managed in the same manner as sarcomas.

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